

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
24 January 2002 (24.01.2002)

PCT

(10) International Publication Number  
**WO 02/06246 A1**

(51) International Patent Classification: C07D 239/557,  
A61K 31/505; C07D 417/04, 409/14, A61P 31/12

(21) International Application Number: PCT/EP01/07955

(22) International Filing Date: 11 July 2001 (11.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0017676.8 19 July 2000 (19.07.2000) GB

(71) Applicant (for all designated States except US): ISTI-  
TUTO DI RICERCHE DI BIOLOGIA MOLECO-  
LARE P. ANGELETTI S.P.A. [IT/IT]; Via Pontina Km.  
30, 600, I-00040 Pomezia (Rome) (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): GARDELLI,  
Cristina [IT/IT]; IRBM, Via Pontina Km. 30, 600,  
I-00040 Pomezia (Rome) (IT). GIULIANO, Claudio  
[IT/IT]; IRBM, Via Pontina Km. 30, 600, I-00040  
Pomezia (Rome) (IT). HARPER, Steven [GB/IT]; IRBM,  
Via Pontina Km. 30, 600, I-00040 Pomezia (Rome) (IT).  
KOCH, Uwe [DE/IT]; IRBM, Via Pontina Km. 30, 600,  
I-00040 Pomezia (Rome) (IT). NARJES, Frank [DE/IT];  
IRBM, Via Pontina Km. 30, 600, I-00040 Pomezia  
(Rome) (IT). ONTORIA ONTORIA, Jesus, Maria  
[ES/ES]; Remei, 10-12, E-08014 Barcelona (ES). POMA,  
Marco [IT/IT]; IRBM, Via Pontina Km. 30, 600, I-00040  
Pomezia (Rome) (IT). PONZI, Simona [IT/IT]; IRBM,

Via Pontina Km. 30, 600, I-00040 Pomezia (Rome) (IT).  
STANSFIELD, Ian [GB/IT]; IRBM, Via Pontina Km. 30,  
600, I-00040 Pomezia (Rome) (IT). SUMMA, Vincenzo  
[IT/IT]; IRBM, Via Pontina Km. 30, 600, I-00040 Pomezia  
(Rome) (IT).

(74) Agent: THOMPSON, John; Merck & Co., Inc., European  
Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex  
CM20 2QR (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,  
ZW.

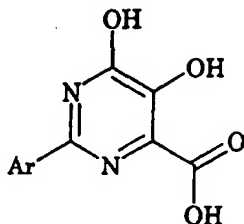
(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- entirely in electronic form (except for this front page) and  
available upon request from the International Bureau

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: DIHYDROXYPYRIMIDINE CARBOXYLIC ACIDS AS VIRAL POLYMERASE INHIBITORS



(I)

(57) Abstract: A class of 2-aryl-4, 5-dihydroxy-6-carboxypyrimidines  
of formula (I): wherein Ar is an optionally substituted aryl or hetero-  
cyclic group; as well as compounds of formula (I) which are deriva-  
tised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy groups;  
and tautomers thereof, and pharmaceutically acceptable salts or esters  
thereof; and inhibitors of viral polymerases, especially the hepatitis C  
virus (HCV) polymerase enzyme.

WO 02/06246 A1

**DIHYDROXYPYRIMIDINE CARBOXYLIC ACIDS AS VIRAL  
POLYMERASE INHIBITORS**

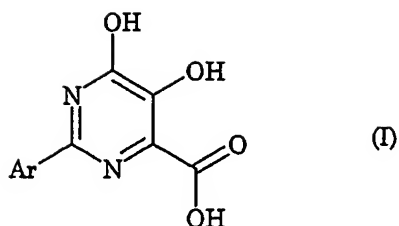
This invention relates to compounds which can act as inhibitors of  
5 viral polymerases, especially the hepatitis C virus (HCV) polymerase, to  
uses of such compounds and to their preparation.

The hepatitis C virus (HCV) is the major causative agent of  
parenterally-transmitted and sporadic non-A, non-B hepatitis (NANB-H).  
Some 1% of the human population of the planet is believed to be affected.  
10 Infection by the virus can result in chronic hepatitis and cirrhosis of the  
liver, and may lead to hepatocellular carcinoma. Currently no vaccine nor  
established therapy exists, although partial success has been achieved in a  
minority of cases by treatment with recombinant interferon- $\alpha$ , either alone  
or in combination with ribavirin. There is therefore a pressing need for  
15 new and broadly-effective therapeutics.

Several virally-encoded enzymes are putative targets for  
therapeutic intervention, including a metalloprotease (NS2-3), a serine  
protease (NS3), a helicase (NS3), and an RNA-dependent RNA polymerase  
(NS5B). Of these, the polymerase plays an essential role in replication of  
20 the virus and is therefore an important target in the fight against  
hepatitis C.

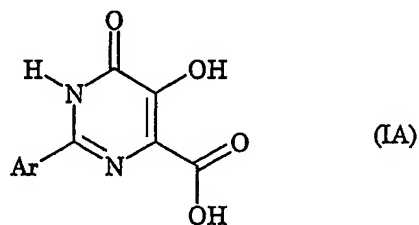
It has now been found that certain 2-aryl-4,5-dihydroxy-6-  
carboxypyrimidines act as inhibitors of hepatitis C virus (HCV)  
polymerase enzyme.

25 According to a first aspect of the present invention there is provided  
a 2-aryl-4,5-dihydroxy-6-carboxypyrimidine of formula (I) below, as well as  
pharmaceutically acceptable salts and esters thereof:



in which Ar is an optionally substituted aryl group.

It will be appreciated that the compound of formula (I) as depicted above may exist in equilibrium with its other tautomeric forms, including  
5 in particular the structure of formula (IA):



wherein Ar is as defined above. It is to be understood that all tautomeric  
10 forms of the compounds of formula (I), as well as all possible mixtures thereof in any proportion, are included within the scope of the present invention.

In a second aspect, the present invention provides a compound of formula (I), or a tautomer thereof, or a pharmaceutically acceptable salt or  
15 ester thereof, for use in therapy, especially for pharmaceutical use in humans.

Before discussing preferred embodiments of the first and second aspects of the invention it is helpful to define certain terms used throughout the specification.

20 By "lower alkyl" and "lower alkoxy" are intended groups having from 1 to 10, preferably 1 to 6, most preferably 1 to 4, carbon atoms. "Lower alkenyl" and "lower alkynyl" groups have from 2 to 10, preferably 2 to 6, carbon atoms.

Typical examples of lower alkyl groups include methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, *tert*-butyl and 1,1-dimethylpropyl. Derived expressions such as "C<sub>1-6</sub> alkoxy" are to be construed accordingly.

Typical examples of lower alkenyl groups include vinyl, allyl and dimethylallyl groups.

Typical examples of lower alkynyl groups include ethynyl and propargyl groups.

Cycloalkyl and cycloalkenyl groups contain from 3 to 8 carbon atoms, preferably 5 to 7. Heterocycloalkyl and heterocycloalkenyl groups are 3 to 8 membered rings which contain one or more heteroatoms selected from O, N and S.

Typical cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Suitable heterocycloalkyl groups include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

The term "aryl" as used herein is intended to encompass heteroaromatic as well as carbocyclic groups and implies an aromatic (or heteroaromatic) ring optionally fused, e.g. benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. Preferred groups containing a carbocyclic aromatic radical have from 6 to 14, more preferably 6 to 10, carbon atoms prior to any optional substitution. Examples of such groups include phenyl and naphthyl. Heteroaryl groups include a 3 to 7 membered heterocyclic aromatic ring consisting of one or more carbon atoms and from one to four heteroatoms selected from nitrogen, oxygen and sulphur. Aryl groups, in general, and prior to any optional substitution, contain from 1 to 14 carbon atoms, preferably 3 to 10 carbon atoms.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl,

dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

Aralkyl and aralkoxy groups generally contain from 2 to 20,  
5 preferably 4 to 15, carbon atoms.

Typical aralkyl groups include benzyl, phenylethyl, phenylpropyl, naphthylmethyl, furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl,  
10 thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl. Derived expressions such as "aralkoxy" are to be construed accordingly.

15 Where a compound or group such as the aryl group, Ar, is described as "optionally substituted" one or more substituents may be present. Optional substituents are not particularly limited and may, for instance, be selected from lower alkyl or alkenyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, aralkyl, lower alkoxy, aryloxy or  
20 aralkoxy, amino, nitro, halo, hydroxy, carboxy, formyl, cyano and trihalomethyl groups. Furthermore, optional substituents may be attached to the compounds or groups which they substitute in a variety of ways, either directly or through a connecting group of which the following are examples: amine, amide, ester, ether, thioether, sulphonamide,  
25 sulphamide, sulphoxide, urea, thiourea and urethane. As appropriate an optional substituent may itself be substituted by another substituent, the latter being connected directly to the former or through a connecting group such as those exemplified above.

In preferred embodiments of the first and second aspects of the  
30 invention the group "Ar" may be selected from the following, all of which may, optionally, be substituted: phenyl, thienyl, oxazolyl, thiazolyl, furyl,

isoquinolinyl, indolyl, isoxazolyl, pyrazolopyrimidinyl and pyrazinyl groups. These groups may be joined to the 2-position of the pyrimidine at any available position of the aryl ring. However, connection at certain positions may be preferred and this is considered in some more detail

5 below.

Preferred optional substituents on the aryl group may be selected from a wide variety of groups. For instance, they may be simple, relatively small groups such as halogen (especially chlorine and bromine), hydroxy, -NO<sub>2</sub>, -NH<sub>2</sub>, -CO<sub>2</sub>H, lower alkyl (especially methyl), lower alkenyl or  
10 alkynyl, -CN, or lower alkoxy (especially methoxy). As appropriate any of these substituents may be substituted by one or more of the others. However, in general at least one substituent is a group of formula (IV):

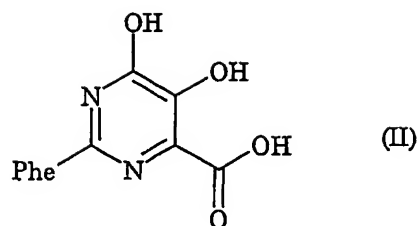


15

where R<sup>3</sup> is a generally hydrophobic moiety containing one or more, but generally at least 3, preferably 4 to 20, particularly 4 to 14, carbon atoms. Preferably, R<sup>3</sup> includes one or more of the following groups, any of which may, optionally, be substituted: aryl, aralkyl, cycloalkyl, lower alkyl  
20 (especially branched lower alkyl), heterocycloalkyl, lower alkenyl, cycloalkenyl and heterocycloalkenyl. The group X is preferably selected from -NH-SO<sub>2</sub>-, -NH-SO<sub>2</sub>-NH-, -CH<sub>2</sub>-SO<sub>2</sub>-, -SO<sub>2</sub>-NH-, -NH-CO-NH-, -NH-CS-NH-, -NH-CO-O-, -NH-CO-, -CO-NH-, -NH-CO-NH-SO<sub>2</sub>-, -NH-CO-NH-CO-, -O-, -S-, -NH-, -CH<sub>2</sub>-, -CH<sub>2</sub>O- and -CH<sub>2</sub>S-.

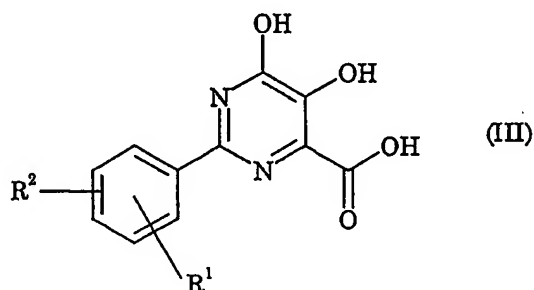
25 The hydrogen atom of any NH group may, optionally, be replaced by a lower alkyl group.

One preferred class of compounds may be represented by formula (II) below:



where Phe is an optionally substituted phenyl group. For instance, examples of compounds within this class are those of formula (III):

5



where each of R<sup>1</sup> and R<sup>2</sup> may independently be selected from H or a substituent group. Preferably, one of R<sup>1</sup> and R<sup>2</sup> is hydrogen, while the other is a substituent. Where a substituent is present it may be at any of the 2-, 3- or 4-positions - i.e. *ortho*, *meta* or *para* to the pyrimidine group. However, where a single substituent is present, substitution at the *ortho* or *meta* positions is preferred.

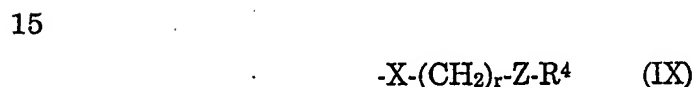
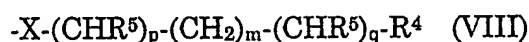
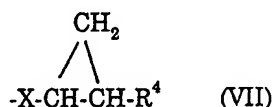
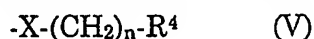
The substituents R<sup>1</sup> and R<sup>2</sup> may be selected from a wide variety of groups. For instance, they may be simple, relatively small groups such as halogen (especially chlorine and bromine), hydroxy, -NO<sub>2</sub>, -NH<sub>2</sub>, -CO<sub>2</sub>H, lower alkyl (especially methyl), lower alkenyl or alkynyl, -CN, or lower alkoxy (especially methoxy). As appropriate any of these substituents may be substituted by one or more of the others.

Although some such compounds are of high activity, it is generally preferable that substituent R<sup>1</sup> and/or R<sup>2</sup> include a relatively hydrophobic group R<sup>3</sup> which is bonded to the phenyl group through a linkage X. In this case the substituents R<sup>1</sup> and/or R<sup>2</sup> may be represented by the formula (IV):



where  $R^3$  and X are as defined above.

5 For instance, examples of preferred classes of compound are those in which a single *ortho* or *meta* substituent is present, and that substituent is selected from the following formulae (V), (VI), (VII), (VIII) and (IX):



wherein

n is zero or an integer from 1 to 6, and preferably is from zero to 3, especially 0 or 1;

20 m is zero or an integer from 1 to 6, but preferably is 0 or 1;

each of p and q is independently 0 or 1, but preferably they are not simultaneously 1;

r is an integer from 1 to 6, preferably 1;

25  $R^4$  is an optionally substituted aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or branched lower alkyl group;

each  $R^5$  is independently a lower alkyl group (especially methyl), a cycloalkyl group, an optionally substituted aryl group (especially phenyl), hydroxy or hydroxy lower alkyl (especially hydroxymethyl), any of which may be optionally etherified, or  $-NH_2$ , optionally protonated, alkylated or  
30 derivatised as a urethane group; and



Z is selected from -O-, -S- and -NH-.

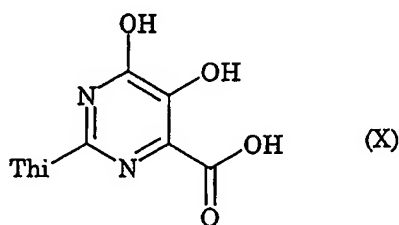
In each of the formulae (IV) to (IX) the linkage X may be any of the X groups specified above.

Among the groups X, the sulfonamide (-NH-SO<sub>2</sub>-), urea  
5 (-NH-CO-NH-), urethane (-NH-CO-O-) and amide (-NH-CO-) groups are most preferred. A particular value of X is -NH-CO-NH-SO<sub>2</sub>-.

The group R<sup>4</sup> is preferably an aryl group, of which optionally substituted phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl and thiazolyl are particularly preferred examples. Each of these may,  
10 optionally, be substituted by another optionally substituted aryl or heteroaryl group of the same or different type.

Examples of compounds of formula (II) can be found in Tables I, II, III and IV. All of the compounds in these Tables have IC<sub>50</sub> values below 100 μM when measured in the assay described below. In many cases the  
15 IC<sub>50</sub> is below 10 μM, and in some cases it is 1 μM or below.

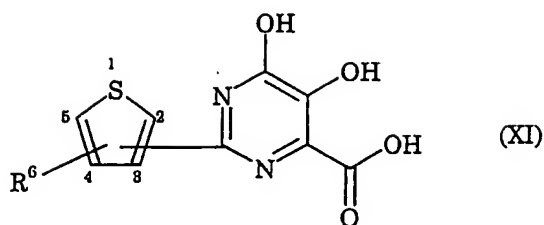
A further preferred class of compounds may be represented by formula (X) below:



20

wherein Thi represents a thienyl group, optionally carrying one or more substituents. Preferred compounds in this class are those in which the thienyl group is unsubstituted, or carries a single substituent R<sup>6</sup>, and may be represented by formula (XI) below:

25



The pyrimidine group and the  $R^6$  substituent may be at any position on the thiophene ring. However, it is preferred that when the pyrimidine is at position 2 on the thiophene ring, then substituent  $R^6$  is at the 3-position, substitution at the 4- or 5-positions being less preferred. When the pyrimidine group is at the 3-position of the thiophene ring, then  $R^6$  is preferably at the 2- or 4-position of the thiophene ring, more preferably at the 4-position.

Substituent  $R^6$  may be selected from a wide variety of groups. For instance, like substituents  $R^1$  and  $R^2$  discussed above it may be a simple, relatively small group such as halogen (especially chlorine and bromine), hydroxy,  $-\text{NO}_2$ ,  $-\text{NH}_2$ ,  $-\text{CO}_2\text{H}$ , lower alkyl (especially methyl), lower alkenyl or alkynyl,  $-\text{CN}$ , or lower alkoxy (especially methoxy). As appropriate any of these substituents may be substituted by one or more of the others.

More preferably, however,  $R^6$  includes a relatively hydrophobic group which is bonded to the thienyl group through a linkage X. In this case, the group  $R^6$  may be represented by the formula (IV):



where X and  $R^3$  are as defined above.

Preferred X groups are amide, sulphonamide, urea and urethane linkages. A particularly preferred X group is  $-\text{NH}-\text{CO}-\text{NH}-\text{SO}_2-$ . Preferred  $R^3$  groups are those shown in formulas (V)-(IX) already discussed above, and which include a group  $R^4$ . Advantageously,  $R^3$  is naphthyl.

Preferred  $R^4$  groups are aromatic groups, especially phenyl, naphthyl, thienyl, pyridyl, benzothienyl, indolyl, benzimidazolyl and

oxazolyl groups. When R<sup>4</sup> comprises fused aromatic rings, the connection to the remainder of the R<sup>3</sup> group may be through any ring.

Preferred optional substituents on R<sup>4</sup>, especially in the case where R<sup>4</sup> is an aryl group, include the following: halogen (e.g. fluorine, chlorine and/or bromine), nitro (-NO<sub>2</sub>), lower alkyl (especially methyl),  
5 trifluoromethyl and aryl (especially phenyl).

Suitably, n is zero.

Suitably, R<sup>4</sup> is naphthyl.

Examples of compounds of formula (X) may be found in Tables V-IX.

10 The compounds exemplified all have IC<sub>50</sub> values of less than 100 μM as measured in the assay described *infra*. In fact, virtually all have an IC<sub>50</sub> of less than 25 μM, mostly less than 10 μM. Very many of the compounds have submicromolar IC<sub>50</sub> values.

Examples of other compounds of formula (I) can be found in Tables  
15 X and XI. The compounds of these Tables have IC<sub>50</sub> values less than 100 μM, some less than 10 μM.

In another aspect, the invention provides compounds of formula (I) which are derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy groups, and tautomers thereof, as well as salts and esters thereof.  
20 These compounds also are suitable for pharmaceutical use.

For instance, either or both of the 4- and 5-hydroxy groups may be etherified, e.g. with an optionally substituted alkyl, aryl or aralkyl group. The 6-carboxy group may be esterified with a variety of alcohols, most preferably an optionally substituted lower alkyl alcohol.

25 Examples of compounds derivatised at the 4-hydroxy, 5-hydroxy or 6-carboxy group are set out in Tables XIIa to XIIc. Although generally less active than the underivatised compounds in the IC<sub>50</sub> assay, the exemplified compounds nevertheless all have IC<sub>50</sub> values below 50 μM.

According to a further aspect of the invention there is provided the  
30 use of a compound of formula (I) above, of a compound of formula (I) which is derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy

groups, of a tautomer thereof, or of a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C virus in a human or animal.

5 A still further aspect of the invention provides a pharmaceutical composition comprising a compound of formula (I) above, a compound of formula (I) which is derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy groups, a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable excipient, diluent or carrier. The composition may be in any suitable form, depending on the  
10 intended method of administration. It may for example be in the form of a tablet, capsule or liquid for oral administration, or of a solution or suspension for administration parenterally.

The pharmaceutical compositions optionally also include one or more other agents for the treatment of viral infections such as an antiviral  
15 agent, or an immunomodulatory agent such as  $\alpha$ -,  $\beta$ - or  $\gamma$ -interferon.

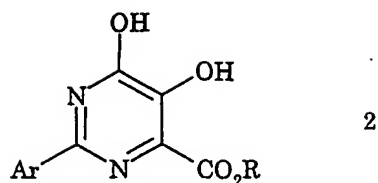
A yet further aspect of the invention provides a method of inhibiting hepatitis C virus polymerase and/or of treating or preventing an illness due to hepatitis C virus, the method involving administering to a human or animal (preferably mammalian) subject suffering from the condition a  
20 therapeutically or prophylactically effective amount of the pharmaceutical composition described above or of a compound of formula (I) above, a compound of formula (I) which is derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy groups, a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof. "Effective amount"  
25 means an amount sufficient to cause a benefit to the subject or at least to cause a change in the subject's condition.

The dosage rate at which the compound, salt or ester is administered will depend on a variety of factors including the activity of the specific compound employed, the metabolic stability and length of  
30 action of that compound, the age of the patient, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug

combination, the severity of the particular condition and the host undergoing therapy. Suitable dosage levels may be of the order of 0.02 to 5 or 10 g per day, with oral dosages two to five times higher. For instance, administration of from 10 to 50 mg of the compound per kg of body weight  
5 from one to three times per day may be in order. Appropriate values are selectable by routine testing. The compound, salt or ester may be administered alone or in combination with other treatments, either simultaneously or sequentially. For instance, it may be administered in combination with effective amounts of antiviral agents,  
10 immunomodulators, anti-infectives or vaccines known to those of ordinary skill in the art. It may be administered by any suitable route, including orally, intravenously, cutaneously and subcutaneously. It may be administered directly to a suitable site or in a manner in which it targets a particular site, such as a certain type of cell. Suitable targeting methods  
15 are already known.

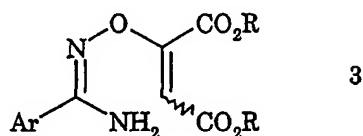
An additional aspect of the invention provides a method of preparation of a pharmaceutical composition, involving admixing at least one compound selected from a compound of formula (I) above, a compound of formula (I) which is derivatised at one or more of the 4-hydroxy, 5-  
20 hydroxy or 6-carboxy groups, a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof, with one or more pharmaceutically acceptable adjuvants, diluents or carriers and/or with one or more other therapeutically or prophylactically active agents.

According to one more aspect of the invention there is provided a  
25 method for the production of compounds of formula (I). These may be prepared by hydrolysis of the corresponding methyl or other ester of formula 2:

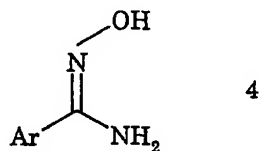


where R is a methyl or other lower alkyl group.

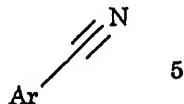
The esters of formula 2 may be prepared by cyclization of oximes of  
 5 formula 3:



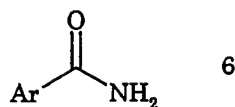
Oximes of formula 3 may be prepared by reaction of amide-oximes of  
 10 formula 4 with diesters of acetylenedicarboxylate:



Amide-oximes of formula 4 may be prepared by reaction of nitriles  
 15 of formula 5 with hydroxylamine:



Nitriles of formula 5 may be obtained from commercial sources or  
 may be prepared from the corresponding primary amides of formula 6  
 20 using established methods known to those skilled in the art:



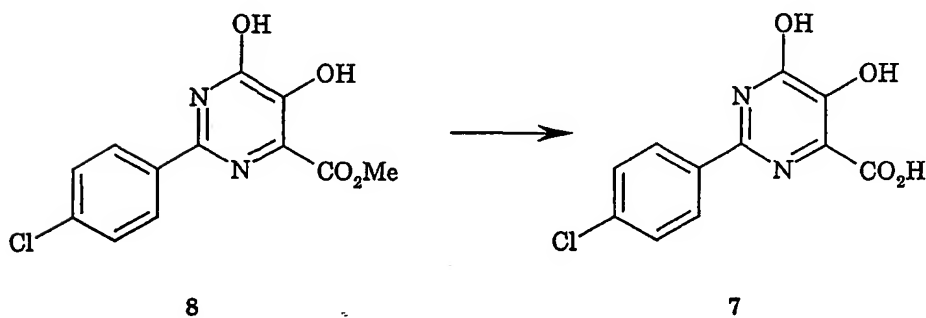
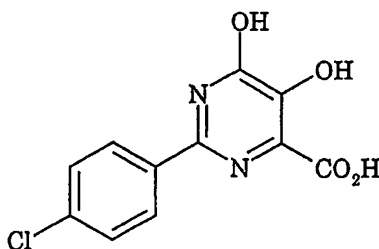
Primary amides of formula 6 may be obtained from commercial sources or may be prepared from the corresponding esters or carboxylic acids using established methods known to those skilled in the art.

Compounds of formula (I) which are derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy groups may be prepared by analogous methods.

Specific procedures are described in the following Examples:

### EXAMPLE 1

#### 2-(4-Chlorophenyl)-4,5-dihydroxypyrimidine-6-carboxylate (7)

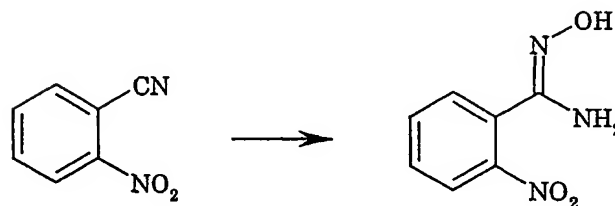
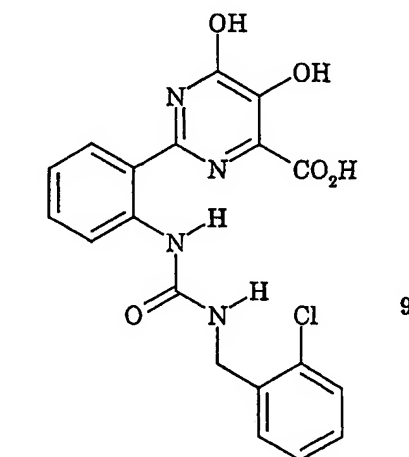


To a suspension of 0.120 g (0.43 mmol) of methyl 2-(4-chlorophenyl)-4,5-dihydroxypyrimidine-6-carboxylate (Aldrich) in 1 ml of MeOH was added 3N NaOH (3 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was acidified by addition of aqueous hydrochloric acid (1N, 5 ml) and the precipitate was filtered off and dried under vacuum to give the title compound (0.11 g, 0.41 mmol, 95% yield).  
5 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.06 (2H, d, *J* 8.54), 8.01 (2H, d, *J* 8.52).

### EXAMPLE 2

10

2-[2-(2-Chlorobenzylureyl)phenyl]-4,5-dihydroxy-6-carboxypyrimidine (9)



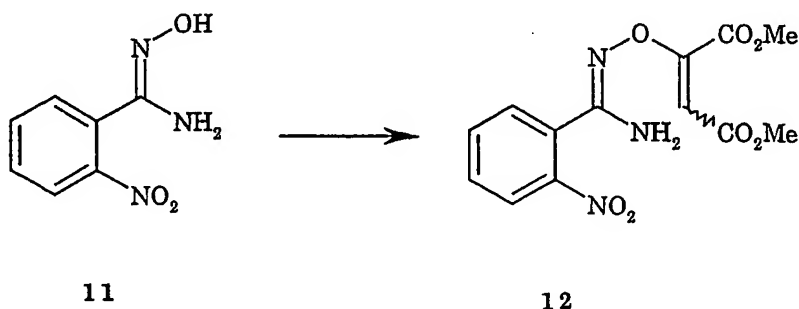
10

11

15 2-Nitrobenzonitrile 10 (10.0 g, 67.51 mmol) was heated at 80°C in water (120 ml) with sodium carbonate (114.77 mmol, 12.164 g) and hydroxylamine hydrochloride (243 mmol, 16.89 g) for 2 h, sufficient EtOH

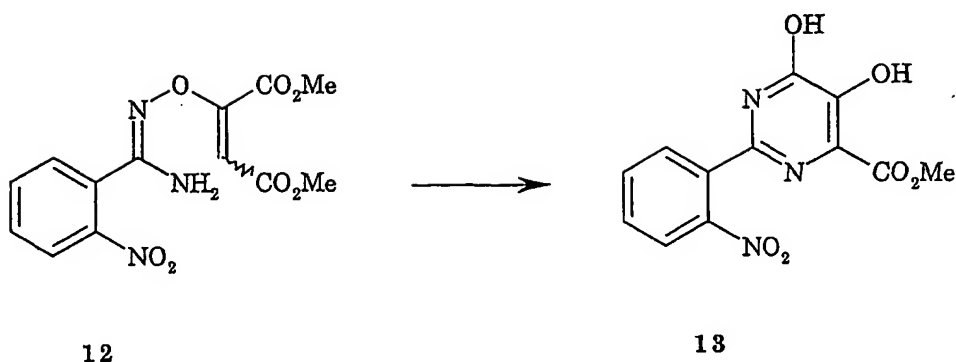


being added to help dissolution of the reaction mixture. The cooled mixture was filtered to remove solids, the aqueous layer was extracted several times with EtOAc, and the extracts were dried and concentrated under reduced pressure. The resulting yellow solid was purified by flash chromatography, or by recrystallization, to give the title compound (50%).  
5  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  9.68 (1H, s), 7.84 (1H, d,  $J$  8), 7.71 (1H, t,  $J$  7.47), 7.64 (1H, d,  $J$  6.3), 7.61 (1H, t,  $J$  8.11), 6.00 (2H, br s). MS  $m/z$  182 ( $M + 1$ ).

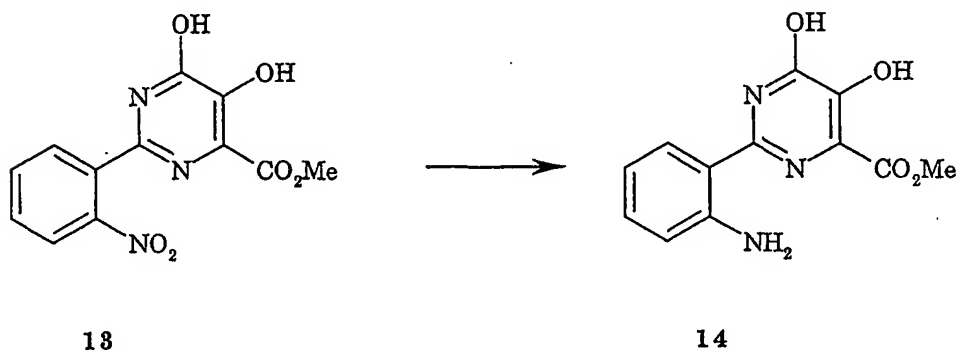


10

A solution of dimethyl acetylenedicarboxylate (2.60 ml, 21.12 mmol, 1.3 eq) and 11 (2.943 g, 16.246 mmol) in  $\text{CHCl}_3$  was heated under reflux for 4 h. After concentration of the solvent the crude product was purified by flash chromatography (eluent 1:1 petroleum ether:ethyl acetate) on silica gel to give 12 as a 1:3.7 mixture of the two geometrical isomers (3.15 g, 60%).  
15  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  8.04 (1H, d,  $J$  7.83), 7.81 (1H, t,  $J$  7.46), 7.75 (1H, t,  $J$  7.39), 7.70 (1H, d,  $J$  7.40 (64%)), 7.64 (1H, d,  $J$  7.48 (36%)), 7.30 (2H, br s (64%)), 6.92 (2H, br s (36%)), 5.70 (1H, s (36%)), 5.53 (1H, s (36%)), 3.78 (3H, s (64%)), 3.73 (3H, s (36%)), 3.59 (3H, s (64%)), 3.55 (3H, s (36%)). MS  $m/z$  324 ( $M + 1$ ).  
20



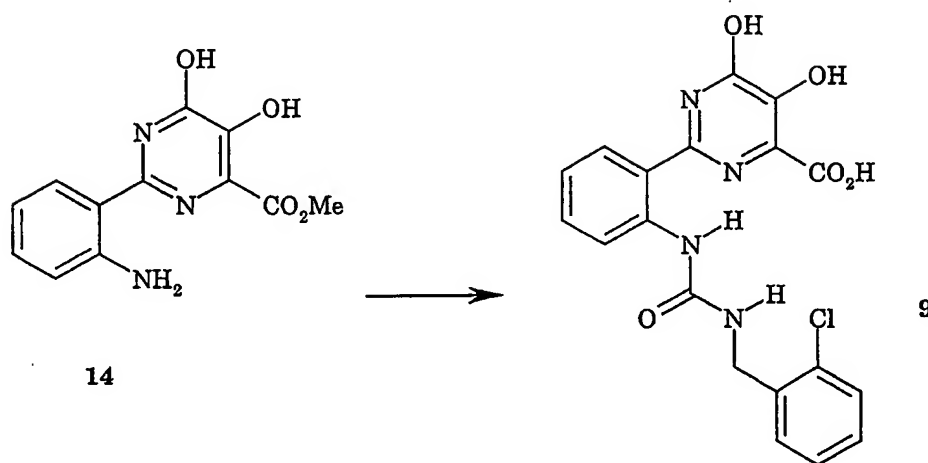
The mixture of adducts 12 (1.28 g, 3.96 mmol) was heated under reflux in *ortho*-xylenes (15 ml) for 6 h. The hot solution was filtered to give  
 5 13 as a yellow solid (0.807 g, 70%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 13.36 (1H, br s), 10.63 (1H, br s), 8.18 (1H, d, *J* 7.97), 7.88 (1H, t, *J* 7.53), 7.80 (1H, d, *J* 7.79), 7.77 (1H, t, *J* 7.56), 3.80 (3H, s). MS *m/z* 292 (*M* + 1).



10

The nitro compound 13 (4.6 g, 15.79 mmol) was dissolved in 450 ml of methanol. Palladium-on-carbon (10% by weight, 200 mg) was added and the mixture was stirred under a hydrogen atmosphere for 2 h. After two hours the reaction was complete (as indicated by reverse-phase tlc)  
 15 and a green solid had precipitated. Dilute hydrochloric acid (1N) was added dropwise until the precipitate had dissolved. The catalyst was removed by filtration, the filtrate was concentrated *in vacuo*, and the resulting solid washed with diethyl ether to give 14 (4.5 g, 96%). <sup>1</sup>H NMR

(DMSO- $d_6$ ):  $\delta$  3.85 (3H, s), 6.77 (1H, bt), 6.94 (1H, d,  $J$  8), 7.24 (1H, t,  $J$  7.4), 7.71 (1H, d,  $J$  8). MS  $m/z$  262 ( $M + 1$ ).



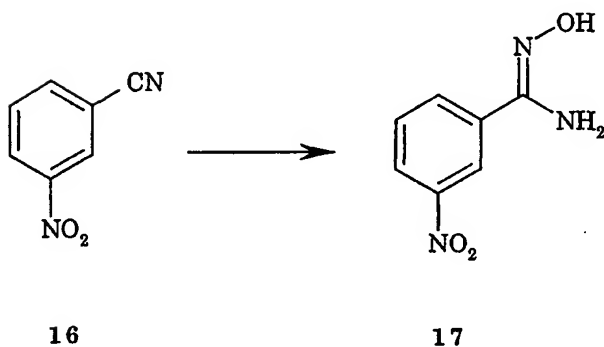
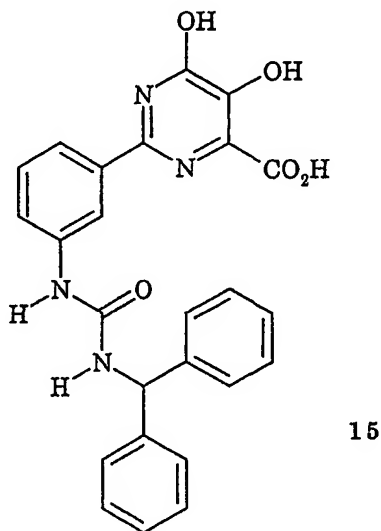
5

The amino-pyrimidine 14 (95 mg, 0.319 mmol) was dissolved in 4 ml of pyridine and 2-chlorobenzyl isocyanate (0.6 ml, 0.419 mmol), dissolved in 2 ml of  $CHCl_3$ , was added dropwise. The mixture was stirred at room temperature overnight. The solution was concentrated *in vacuo* and the resulting solid washed with HCl (1N), MeOH and diethyl ether to give 75 mg (53%) of ester urea which was used without further purification.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  3.80 (3H, s), 4.36 (2H, d,  $J$  5.8), 6.99-7.04 (2H, m), 7.28-7.44 (5H, m), 7.64 (1H, d,  $J$  7.8), 8.23 (1H, d,  $J$  8.10), 10.30 (1H, s), 10.60 (1H, br s), 13.00 (1H, br s). MS  $m/z$  429 ( $M + 1$ ).

To the ester urea was added a 0.5 M solution of NaOH (2 ml) and the resulting mixture was heated under reflux for 30 min. To the cooled solution, HCl (1N) was added dropwise, and a solid precipitate formed. The solid was isolated by filtration, then washed with methanol and diethyl ether to give 31 mg (43 %) of the title compound.  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  4.35 (2H, d,  $J$  5.8), 6.93 (1H, bt), 7.00 (1H, t,  $J$  7.4), 7.27-7.43 (5H, m), 7.68 (1H, d,  $J$  7.8), 8.22 (1H, d,  $J$  8.2), 10.90 (1H, s), 12.90 (1H, s). MS  $m/z$  415 ( $M + 1$ ).

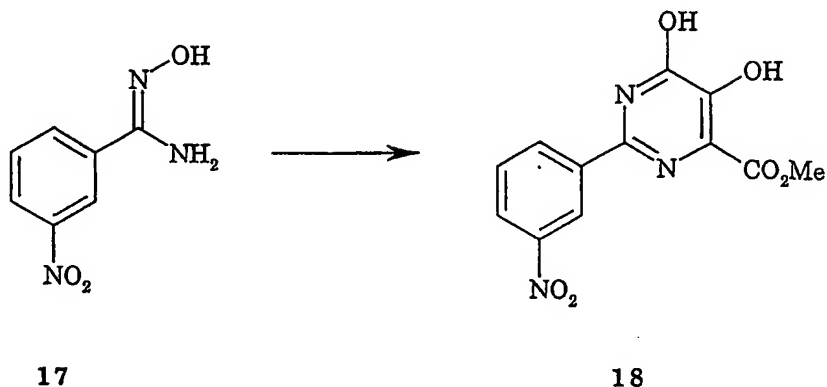
**EXAMPLE 3****2-[3-(Diphenylmethylureyl)phenyl]-4,5-dihydroxy-6-carboxypyrimidine**  
**(15)**

5



A mixture of 3-nitrobenzonitrile 16 (20 g, 135 mmol) and hydroxylamine hydrochloride (46.9 g, 675 mmol) in a water/ethanol mixture (600 ml, 5:1) was heated to 60°C under vigorous stirring. Sodium carbonate (35.8 g, 337.5 mmol) was added portionwise and the temperature was increased to 100°C. The mixture was stirred at 100°C for 1.5 h. When cooled to room temperature, a solid precipitated which was isolated by filtration to give amidoxime 17 (24 g) as yellow crystals (98%).

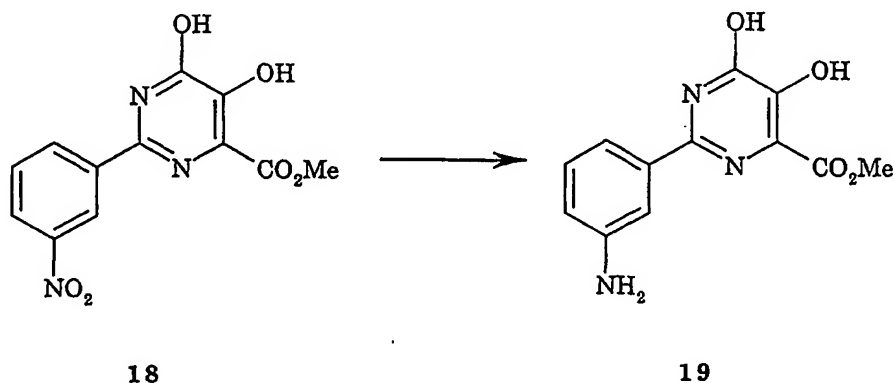
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.94 (1H, s), 8.50 (1H, s), 8.35 (1H, d,  $J$  8), 8.15 (1H, d,  $J$  8), 7.67 (1H, t,  $J$  8), 6.07 (3H, s). MS  $m/z$  182 ( $M+1$ ).



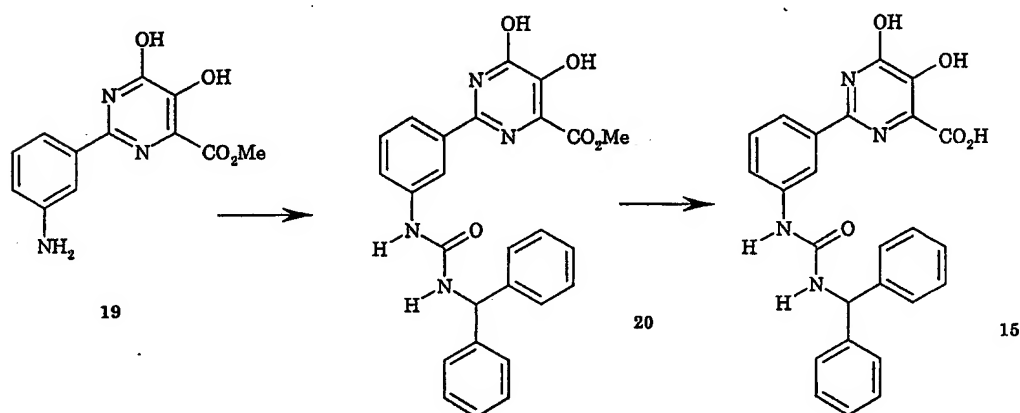
5

A mixture of amidoxime 17 (22 g, 121.5 mmol) and dimethyl acetylenedicarboxylate (16.4 ml, 133.6 mmol) in a chloroform/methanol mixture (200 ml, 3:1) was refluxed for 3 h which gave a brown solution. The solution was concentrated *in vacuo* and the resulting oil was dissolved in xylene (150 ml), heated under reflux for 4 h at which point there was precipitation of a solid. The mixture was cooled to room temperature and the solid was isolated by filtration and dried *in vacuo* to give a brown solid (31 g) that was recrystallized from hot acetic acid (150 ml) to give 18 (28 g, 72%).  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  13.43 (1H, br s), 10.71 (1H, br s), 8.86 (1H, s), 8.44 (1H, d,  $J$  8), 8.36 (1H, d,  $J$  8), 7.80 (1H, t,  $J$  8), 3.87 (3H, s). MS  $m/z$  292 ( $M+1$ ).

10  
15



A mixture of compound 18 (2.1 g) and 10% palladium-on-carbon in a mixture of methanol and ethyl acetate (250 ml, 4:1) was stirred under atmospheric pressure of hydrogen overnight. The catalyst was removed by filtration and the catalyst was washed with hot tetrahydrofuran (4 x 100 ml). The combined filtrate and washings were concentrated *in vacuo* giving 19 as pale yellow solid (1.87 g, quantitative). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 11.89 (1H, br s), 10.45 (1H, br s), 7.17 (1H, s), 7.10-7.08 (1H, m), 6.66-6.69 (1H, m), 5.32 (2H, br s), 3.83 (3H, s). MS m/z 262 (M+1).



Diphenylmethyl isocyanate (1.2 eq) was added neat to a 0.1N solution of pyrimidine 19 (100 mg) in dry pyridine stirring at room temperature overnight in a 15 ml centrifuge tube. Solvent was removed *in vacuo* using a Speedvac and the resulting solid triturated with 1N hydrochloric acid (3 x 5 ml), methanol (3 x 5 ml), diethyl ether (3 x 5 ml), and solid separated by centrifugation (5 min at 4000 rpm) and dried under vacuum. The residue (ester 20) was suspended in 2.5 eq of 0.5N sodium hydroxide and stirred at 65°C for 20 min. The pH was adjusted to 3.5 with 1N hydrochloric acid which precipitated a solid. The solid was separated by centrifugation and the residue triturated with water (3 x 5 ml), methanol (3 x 5 ml) and diethyl ether (3 x 5 ml) using centrifuge each time

to separate the solid. Removal of the remaining solvent under high vacuum gave desired free acid **15** as a white solid.

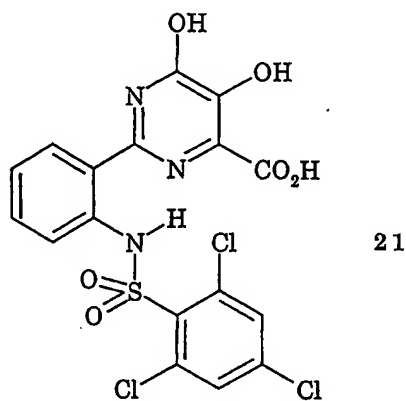
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of **20**: δ 13.05 (1H, br s), 8.65 (1H, s), 7.92 (1H, s), 7.59 (1H, d, *J* 8), 7.52 (1H, d, *J* 8), 7.37-7.16 (12H, m), 5.91 (1H, d, *J* 8), 3.79 (3H, s). MS *m/z* 471 (M+1).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) of **15**: δ (1H, br s), 8.67 (1H, s), 7.93 (1H, s), 7.59 (1H, d, *J* 8), 7.52 (1H, d, *J* 8), 7.37-7.16 (12H, m), 5.96 (1H, d, *J* 8). MS *m/z* 457 (M+1).

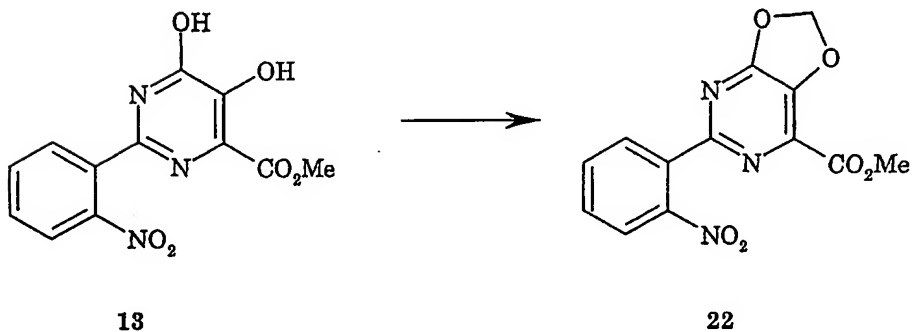
10

#### EXAMPLE 4

2-[2-(2,4,6-Trichlorophenylsulfonylamino)phenyl]-4,5-dihydroxy-6-carboxypyrimidine (21)

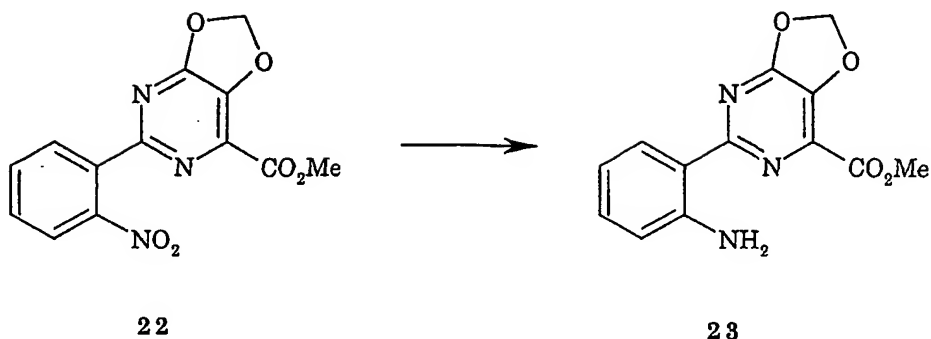


15



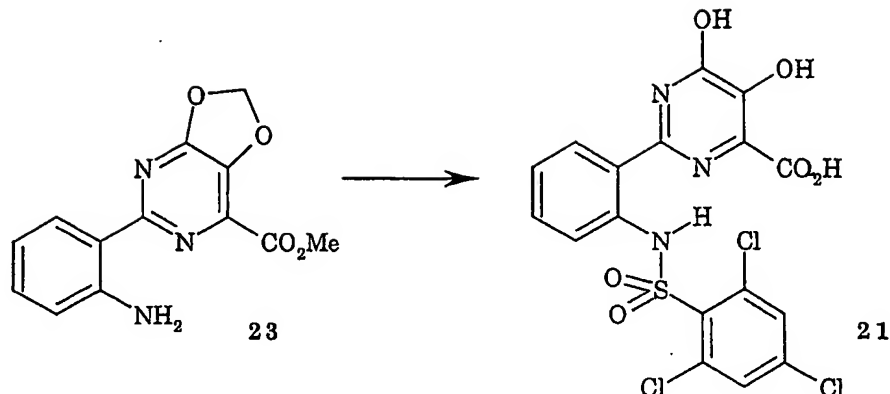
Cesium fluoride (12.1 g, 79.7 mmol) was added to methyl 2-(2-nitrophenyl)-4,5-dihydroxy-6-carboxylate (**13**) (4.6 g, 15.8 mmol) in *N,N*-dimethylformamide (120 ml) at room temperature under nitrogen and the resultant suspension stirred vigorously for 20 min. Dibromomethane (1.2 ml, 17.1 mmol) was introduced and the reaction immersed in a pre-heated oil bath at 120°C. After 30 min, a further aliquot of dibromomethane (1.2 ml, 17.1 mmol) was added and heating continued for another 30 min. Additional dibromomethane (0.6 ml, 8.6 mmol) was introduced and heating continued for a further 20 min before the reaction was allowed to cool to room temperature and partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organics washed with 1N aqueous hydrochloric acid, water and then brine. The organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to leave a brown foam. Flash chromatography on silica gel (using 40% ethyl acetate/petroleum ether as eluent) gave the cyclic methyleneacetal (**22**) as an off-white powder (2.92 g, 61%):  $R_f$  (40% ethyl acetate/petroleum ether) = 0.25;  $^1\text{H}$  NMR (DMSO- $d_6$ ; 400 MHz):  $\delta$  7.94 (1H, dd,  $J$  7.7, 1.2, (O<sub>2</sub>N)CCH or (pyrimidine)CCH), 7.93 (1H, dd,  $J$  7.7, 1.5, (O<sub>2</sub>N)CCH or (pyrimidine)CCH), 7.80 (1H, td,  $J$  7.7, 1.2, (pyrimidine)CC(H)CH or (O<sub>2</sub>N)CC(H)CH), 7.71 (1H, td,  $J$  7.7, 1.5, (pyrimidine)CC(H)CH or (O<sub>2</sub>N)CC(H)CH), 6.40 (2H, s, OCH<sub>2</sub>O), 3.88 (3H, s, CO<sub>2</sub>Me);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ; 75.5 MHz):  $\delta$  167.8, 162.0, 153.4, 149.1, 140.5, 132.5, 130.9, 130.8, 130.7, 129.1, 124.0, 102.7, 52.5;  $m/z$  (ES+) 326 (55%, [M + Na]<sup>+</sup>), 304 (100%, [M + H]<sup>+</sup>), 272 (20%), 243 (10%), 198 (15%), 186 (15%), 134 (25%).





A slurry of palladium on carbon (300 mg, 10% Pd/C) in ethyl acetate (20 ml) was added under nitrogen to the 2-nitrophenylpyrimidine (**22**) (3.5 g, 11.6 mmol) in ethyl acetate (330 ml). The reaction was stirred vigorously under a hydrogen atmosphere overnight (14 h). The catalyst was removed by filtration on a glass fibre filter, washing thoroughly with warm ethyl acetate and methanol. The resultant yellow solution was concentrated *in vacuo* to afford the aniline (**23**) as a yellow solid (3 g, 95%):

$R_f$  (40% ethyl acetate/petroleum ether) = 0.38;  $^1\text{H}$  NMR (DMSO- $d_6$ ; 400 MHz):  $\delta$  8.11 (1H, dd,  $J$  8.1, 1.6, (pyrimidine)CCH), 7.29 (2H, br s,  $\text{NH}_2$ ), 7.12 (1H, td,  $J$  7.6, 1.6, ( $\text{H}_2\text{N}$ )CC(H)CH), 6.76 (1H, d,  $J$  8.1, ( $\text{H}_2\text{N}$ )CCH), 6.56 (1H, t,  $J$  7.6, (pyrimidine)CC(H)CH), 6.32 (2H, s,  $\text{OCH}_2\text{O}$ ), 3.91 (3H, s,  $\text{CO}_2\text{Me}$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ ; 75.5 MHz):  $\delta$  167.4, 162.7, 157.3, 149.3, 138.3, 131.4, 129.6, 127.3, 116.8, 115.8, 114.9, 101.9, 52.8;  $m/z$  (ES+) 296 (10%,  $[\text{M} + \text{Na}]^+$ ), 274 (100%,  $[\text{M} + \text{H}]^+$ ), 214 (40%), 186 (30%), 158 (40%), 131 (50%), 118 (65%).



Triethylamine (80  $\mu$ l, 0.574 mmol) was added to the aniline (23) (50 mg, 0.183 mmol) and 2,4,6-trichlorobenzenesulfonyl chloride (Maybridge)

5 (103 mg, 0.368 mmol) in dry acetonitrile (4 ml). The reaction was agitated on an orbital shaker at room temperature overnight followed by removal of volatiles *in vacuo* in a SpeedVac to afford a brown solid. The solid was suspended in a mixture of 1,4-dioxane (2 ml) and 2N aqueous sodium hydroxide (1 ml, 2 mmol). The reaction was heated, with stirring, at 70°C

10 for 2 h, then acidified with 4N aqueous hydrochloric acid (1 ml, 4 mmol) and stirred at room temperature for 30 min. The reaction was concentrated *in vacuo* in a SpeedVac to leave a tan coloured gum. Iterative washing, centrifugation and decanting of the supernatants using first water (3 washings), and then diethyl ether (2 washings), followed by

15 lyophilization (acetonitrile/water) afforded the title compound (21) in crude form as an off-white powder (45 mg, 50%). Purification by reverse phase HPLC (Merck Hibar 250-25, LiChrosorb RP-18 (7  $\mu$ m) column, using acetonitrile and water (both containing 0.1% trifluoroacetic acid) as eluent gave the title compound (21) as a white powder following lyophilization (21

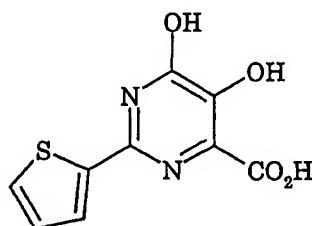
20 mg, 23%).  $^1\text{H}$  NMR (DMSO- $d_6$ ; 400 MHz):  $\delta$  12.90 (1.5H, br s,  $\text{NH}$  or  $\text{OH}$ ), 7.85 (1H, d,  $J$  8.0, (pyrimidine) $\text{CCH}$ ), 7.81 (2H, s, (Cl) $\text{CCH}$ ), 7.42-7.39 (2H, m, ( $\text{O}_2\text{SNH}$ ) $\text{CCH}$  and (pyrimidine) $\text{CC(H)CH}$  or ( $\text{O}_2\text{SNH}$ ) $\text{CC(H)CH}$ ), 7.18-7.14 (1H, m, (pyrimidine) $\text{CC(H)CH}$  or ( $\text{O}_2\text{SNH}$ ) $\text{CC(H)CH}$ );  $m/z$  (ES-) 515, 513, 511 chlorine isotope cluster (5%, 15%, 15%,  $[\text{M} + \text{Na} - 1]^-$ ), 492, 490, 488

chlorine isotope cluster (15%, 35%, 35%, [M-1]<sup>-</sup>), 448, 446, 444 chlorine isotope cluster (10%, 25%, 20%, [M-CO<sub>2</sub>H]<sup>-</sup>).

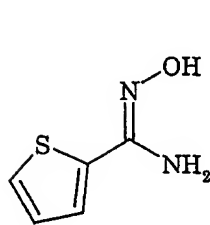
### EXAMPLE 5

5

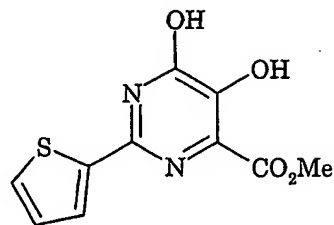
#### 2-(2-Thienyl)-4,5-dihydroxypyrimidine-6-carboxylate (24)



24

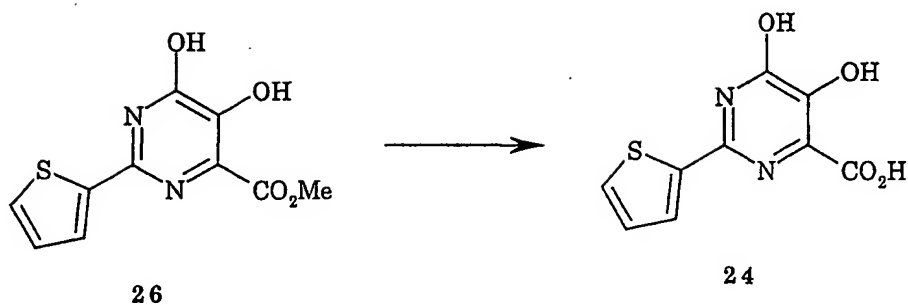


25



26

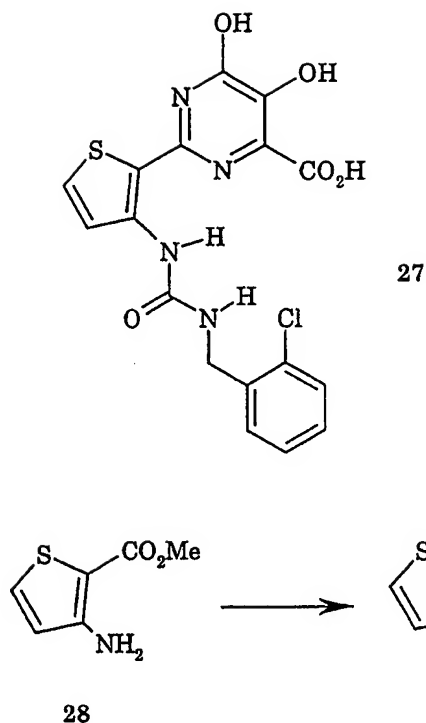
10           A solution of 2-thiophene amidoxime 25 (1.00 g, 7.03 mmol) in  
chloroform (5 ml) was treated dropwise with dimethyl  
acetylenedicarboxylate (1.00 g, 7.17 mmol) and the resulting solution was  
stirred at room temperature for 2 h. The mixture was concentrated *in*  
*vacuo* to give a residue which was taken up in *p*-xylene (5 ml) and heated  
15   under reflux for 5 h. The mixture was cooled to room temperature and the  
precipitate was collected by filtration. After washing with methanol and  
diethyl ether the precipitate was crystallized from acetic acid to afford  
methyl 2-(2-thienyl)-4,5-dihydroxypyrimidine-6-carboxylate 26 (470 mg,  
26%) as a solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 13.20 (1H, bs), 10.48 (1H, bs), 7.99  
20   (1H, d, *J* 3.5), 7.76 (1H, d, *J* 5), 7.16 (1H, dd, *J* 5, 3.5), 3.84 (3H, s).



A suspension of methyl 2-(2-thienyl)-4,5-dihydroxypyrimidine-6-carboxylate **26** (300 mg, 1.19 mmol) in 1N aqueous sodium hydroxide (2 ml) was heated at 50°C for 3 h. The resulting mixture was cooled to room temperature and acidified with 1N aqueous hydrochloric acid. The precipitate was collected and washed with water and diethyl ether, and dried to give the title compound **24** (212 mg, 75%) as a brown solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.40 (1H, bs), 7.84 (1H, d, *J* 4), 7.61 (1H, d, *J* 5.5), 7.09 (1H, dd, *J* 5.5, 4). <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 169.0, 161.6, 156.0, 138.4, 136.1, 136.2, 128.9, 127.8, 125.7. MS *m/z* (MH)<sup>+</sup> 239.0.

### EXAMPLE 6

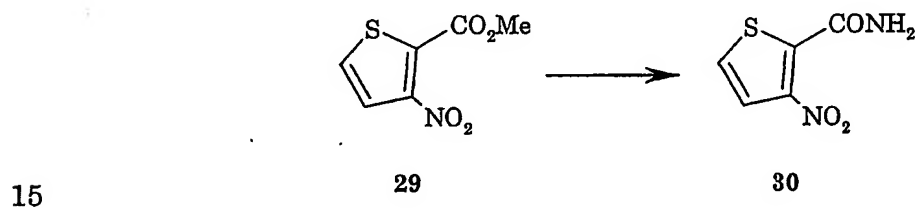
2-[3-(2-Chlorophenylmethylaminocarbonylamino)thien-2-yl]-4,5-dihydroxypyrimidine-6-carboxylate (27)



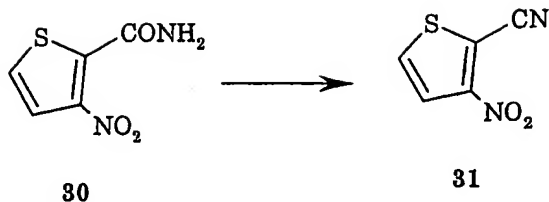
A modification of the method described by Huddleston (*Synth. Commun.*, 1995, 25, 3729) was used, as follows:

- 5 Commercial methyl 3-amino-2-thiophenecarboxylate 28 (75 g, 0.48 mol) was suspended in water (125 ml) and treated with concentrated hydrochloric acid (125 ml). The resulting suspension was stirred for 45 min at room temperature then cooled to -10°C with an ice/salt bath (internal thermometer). A solution of sodium nitrite (33 g, 0.48 mol) in
- 10 water (80 ml) was carefully added *via* dropping funnel, while internal temperature was kept between -5 and 0°C. After the addition, the reaction mixture was stirred for 1 h at 0°C, then treated in one portion with a solution of sodium tetrafluoroborate (79 g, 0.72 mol) in water (150 ml). The precipitated salt was isolated by filtration, washed with cold 5%
- 15 aqueous sodium tetrafluoroborate (2 x 180 ml), ethanol (2 x 180 ml) and diethyl ether (2 x 180 ml), then dried in the air. The beige solid (98.5 g, 81%) thus obtained was used without further purification.

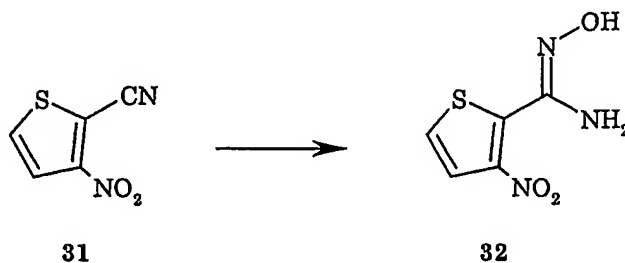
Activated copper bronze (19.1 g, 0.3 mol; see Vogel: *Practical Organic Chemistry*, p. 426 for activation) was added to a mechanically stirred solution of sodium nitrite (82.8 g, 1.2 mol) in water (180 ml). A suspension of the foregoing salt (25.6 g, 0.1 mol) in water (100 ml) was added to the vigorously stirred mixture portionwise over 1 h at room temperature. After the addition, stirring was continued for another hour. The reaction mixture was diluted with dichloromethane (500 ml) and filtered through diatomaceous earth (Celite). After separation of the phases, the aqueous phase was extracted with dichloromethane (4 x 300 ml) and the combined organic layers were dried over sodium sulfate in the presence of activated charcoal. Filtration and evaporation afforded 17.3 g (92%) of a red solid, which was used without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.48 (1H, d, *J* 5), 7.43 (1H, d, *J* 5), 3.90 (3H, s).



The ester **29** (25 g, 0.13 mol), prepared as described above, was stirred for 24 h at 100°C in a well-closed Pyrex bottle in the presence of 2M methanolic ammonia (405 ml, 0.8 mol). The volatiles were removed *in vacuo* and the residue crystallized from hot ethyl acetate to afford 16.5 g (74%) of 3-nitrothiophene-2-carboxamide **30**. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.21 (1H, bs), 7.91 (1H, bs), 7.73 (1H, d, *J* 5), 7.57 (1H, d, *J* 5), 3.28 (3H, s). An analytical sample was obtained by further recrystallization from ethyl acetate; elemental analysis, calc. for C<sub>5</sub>H<sub>4</sub>N<sub>2</sub>O<sub>3</sub>S: C, 34.88; H, 2.34; N, 16.27. Found: C, 34.75; H, 2.24; N, 15.96.



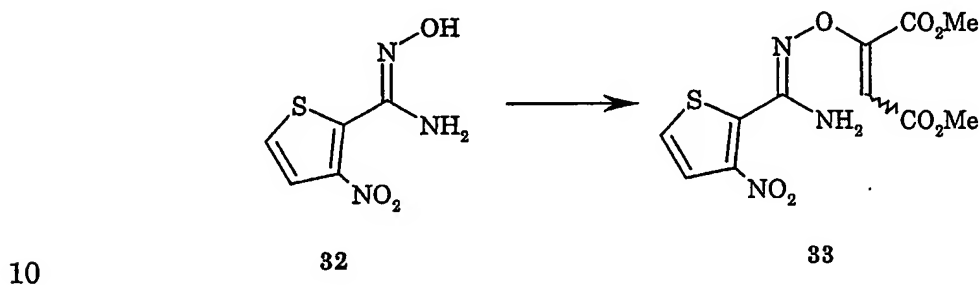
The amide **30** (15.5 g, 90 mmol), prepared as described above, was dissolved in dichloromethane (700 ml). Triethylamine (27.2 g, 37.6 ml, 270 mmol) was added and the solution cooled to 0°C. After dropwise addition of neat trifluoroacetic anhydride (24.6 g, 16.5 ml, 117 mmol), the reaction was allowed to warm to room temperature and stirred for 1 h. The solution was concentrated *in vacuo*, the residue taken into ethyl acetate and then washed successively with hydrochloric acid (1N, 2 x), water (1 x), saturated aqueous sodium hydrogencarbonate (2 x) and brine. Drying over sodium sulfate and removal of solvent gave a dark solid, which was purified by flash chromatography (400 g of silica gel, petroleum ether:ethyl acetate 7:3 + 1% MeOH as eluent) yielding 2-cyano-3-nitrothiophene **31** (13.4 g, 96.5%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.75 (1H, d, *J* 5.5), 7.68 (1H, d, *J* 5.5). An analytical sample was obtained by recrystallization from dichloromethane/*n*-pentane, m.p. 87-88°C; elemental analysis, calc. for C<sub>5</sub>H<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S: C, 38.96; H, 1.31; N, 18.17; S, 20.80. Found: C, 38.92; H, 1.20; N, 18.03; S, 21.31.



The nitrile **31** (86.93 mmol, 13.4 g), prepared as described above, was suspended in water (360 ml) and ethanol (48 ml). Sodium carbonate (15.7 g, 147.8 mmol) and hydroxylamine (18.7 g, 287 mmol) were added

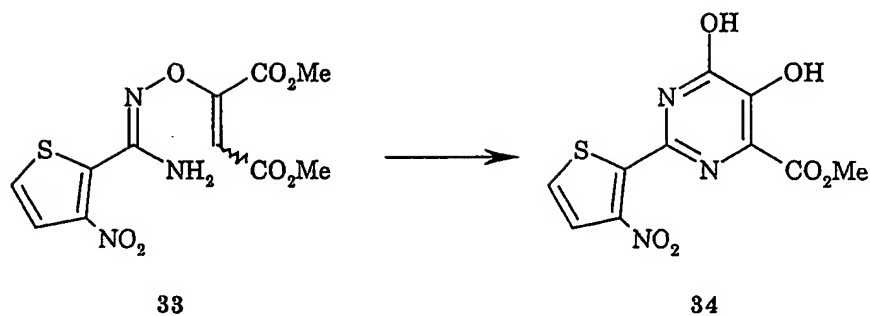
and the mixture was left at room temperature for 24 h. The orange solid was isolated by filtration, washed with a small portion of diethyl ether and dried. The amidoxime **32** (14.0 g, 86%) was obtained as an orange solid.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 9.95 (1H, bs), 7.68 (1H, d, *J* 5.3), 7.60 (1H, d, *J* 5.3),  
5 6.08 (2H, bs). MS (ESI) 188 [M+H]<sup>+</sup>. An analytical sample was obtained by recrystallization from dichloromethane/*n*-pentane, m.p. 201-202°C; elemental analysis, calc. for C<sub>5</sub>H<sub>5</sub>N<sub>3</sub>O<sub>3</sub>S: C, 32.09; H, 2.69; N, 22.45; S, 17.13. Found: C, 32.34; H, 2.64; N, 21.96; S, 17.47.

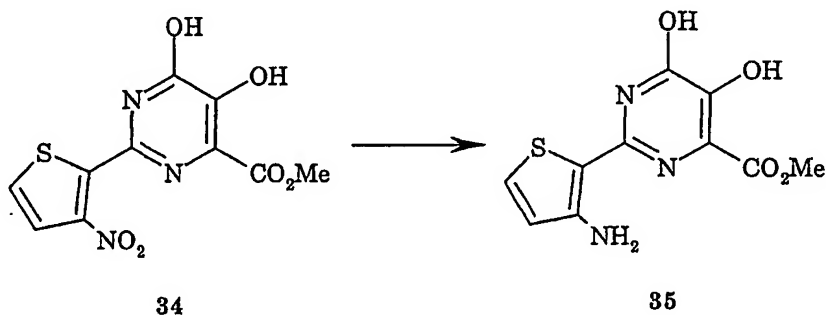


The amidoxime **32** (11.87 g, 63.90 mmol), prepared as described above, was suspended in dichloromethane (250 ml). Triethylamine (0.5 ml) and dimethyl acetylenedicarboxylate (9.53 g, 67.1 mmol, filtered over  
15 basic alumina) were added. The mixture was refluxed for 3 h and became homogeneous during this time. Evaporation of the dichloromethane gave a red oil (20.88 g), which was dissolved in ethyl acetate (400 ml). After washing with water and brine, the organic phase was dried over sodium sulfate and the solution was concentrated *in vacuo*. The residual oil (20.5  
20 g, 97%) was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>), two diastereomers (2.5:1\*): δ 7.61\*, 7.58 (1H, d, *J* 5.6), 7.38\*, 7.33 (1H, d, *J* 5.6), 6.10, 5.84\* (2H, bs), 5.94, 5.88\* (1H, s), 3.90\*, 3.83 (3H, s), 3.71, 3.68\* (3H, s). MS (ESI) 330 [M+H]<sup>+</sup>, 352 [M+Na]<sup>+</sup>.



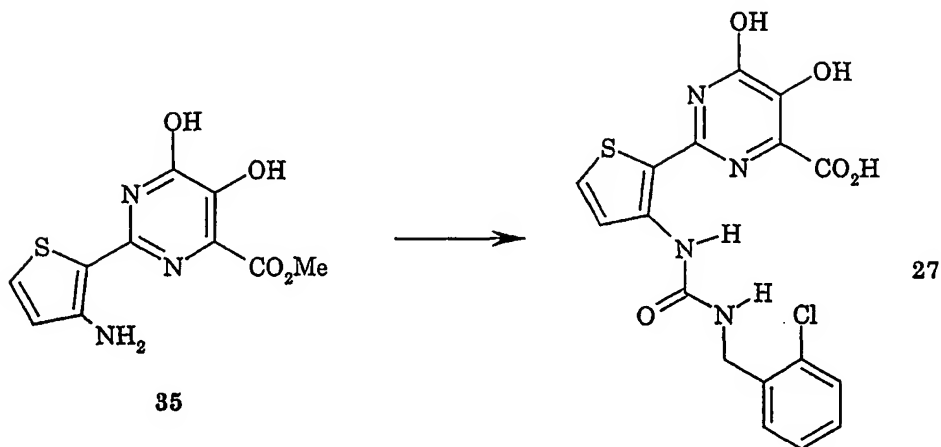


To a flask containing the oxime 33 (30.7 g, 93.28 mmol), prepared as described above, was added xylene (212 ml). The reaction was heated at 140°C until the disappearance of the starting material was evident by TLC (7 h). The reaction mixture was stored in a refrigerator at 4°C overnight and the precipitate isolated by filtration. The solid was washed with ethyl acetate and petroleum ether and dried *in vacuo*. The product was obtained as an off-white powder (13.27 g, 48%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 13.30 (1H, bs), 11.80 (1H, bs), 7.89 (1H, d, *J* 5.4), 7.71 (1H, d, *J* 5.4), 3.82 (3H, s). MS (ESI) 296 [M-H]. (In addition to the desired product, the <sup>1</sup>H NMR spectrum in DMSO showed about 6% of a dehydroxylated product).



The pyrimidine 34 (1.5 g, 5.05 mmol), prepared as described above, was dissolved in a mixture of ethyl acetate and methanol (2:1, 200 ml). Palladium-on-charcoal (10% Pd, 1.5 g) was added, and the reaction stirred under an atmosphere of hydrogen for 5 h at ambient temperature. The catalyst was removed by filtration and washed with hot ethyl acetate and methanol. After evaporation the amine 35 (1.08 g, 80%) was obtained as a

yellow solid.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  8.80 (3H, bs), 7.48 (1H, d,  $J$  5.2), 6.67 (1H, d,  $J$  5.2), 3.85 (3H, s). MS (ESI) 268  $[\text{M}+\text{H}]^+$ .



5

The amine 35 (300 mg, 1.12 mmol), prepared as described above, was dissolved in pyridine (10 ml). Commercial 2-chlorobenzyl isocyanate (225 mg, 1.34 mmol) was added dropwise. The reaction was monitored by analytical HPLC. After consumption of amine, the solution was

10 concentrated *in vacuo* and the residue was dissolved in a large volume of ethyl acetate, washed with hydrochloric acid (1N), brine, and dried over sodium sulfate. The compound (methyl ester) obtained after concentration of the solution *in vacuo* was hydrolyzed using sodium hydroxide (4.5 ml, 1N) and methanol (3 ml) at 80°C for 30 min. The solution was then cooled

15 in an ice-bath and acidified with hydrochloric acid (1N) to pH 2. The precipitated solid was isolated by filtration, washed with water and diethyl ether and dried. It was boiled once in ethyl acetate, filtered and washed again with ethyl acetate and diethyl ether, and dried *in vacuo* to give the crude product. This was purified by preparative reversed phase HPLC

20 using a Waters Prep-NovaPak column (HR C18, 40 x 100 mm, 6 micron) and 0.05% trifluoroacetic acid in water (solvent A) and 0.05% trifluoroacetic acid in acetonitrile (solvent B) as eluents; gradient: 80% A, 2 min isocratic, in 2 min to 60% A, then in 8 min to 30% A; flow 35 ml/min,

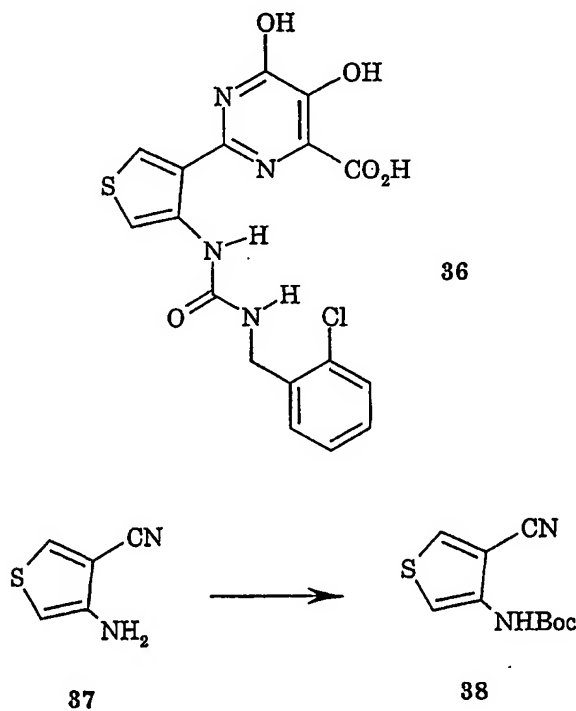
giving 105 mg (22%) of the title compound as a yellow powder after lyophilization.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  12.70 (1H, bs), 11.05 (1H, bs), 8.80, 7.83 (1H, d,  $J$  5.4), 7.61 (1H, d,  $J$  5.4), 7.45 (2H, m), 7.36 (2H, m), 7.00 (1H, bs), 4.42 (2H, bd,  $J$  5.9). MS (ESI) 421, 419 [M-H].

5

### EXAMPLE 7

2-[4-(2-Chlorophenylmethylaminocarbonylamino)thien-3-yl]-4,5-dihydroxypyrimidine-6-carboxylate (36)

10

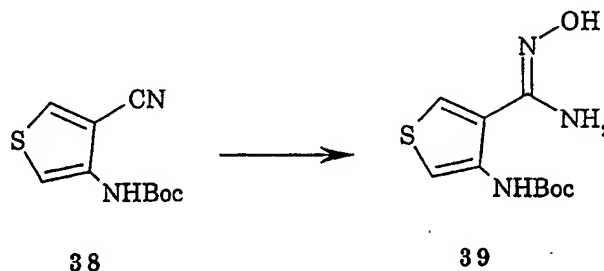


A solution of 3-amino-4-cyanothiophene 37 (10 g, 80.5 mmol) in methylene chloride (125 ml) was treated with pyridine (7.5 ml) and di-*tert*-butyl dicarbonate (36.9 g, 169.14 mmol) then heated under reflux for 45 min. The cooled solution was concentrated *in vacuo* and the residue was diluted with 1N hydrochloric acid. After extraction with ethyl acetate (3 x 150 ml) the dried organic layer was concentrated *in vacuo* to give 3-*tert*-

15

butyloxycarbonylamino-4-thiophene carbonitrile **38** (15 g, 83%) as a solid.

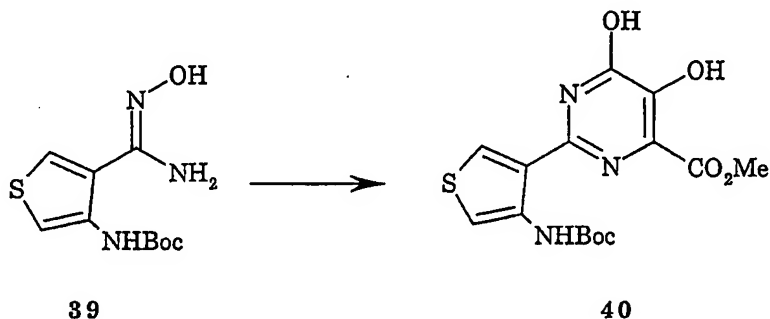
$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  9.35 (1H, bs), 8.42 (1H, s), 7.41 (1H, s), 1.47 (9H, s).



5

A solution of *N*-Boc-3-amino-4-cyanothiophene (3.04 g, 13.5 mmol) and hydroxylamine hydrochloride (1.32 g, 69.5 mmol) in MeOH (25 ml) was treated with  $\text{Et}_3\text{N}$  (2.32 g, 23 mmol) and heated at  $50^\circ\text{C}$  for 12 h. The solution was cooled and concentrated, and the residue was taken up with  $\text{H}_2\text{O}$  and AcOEt. The organic layer was separated and dried, then concentrated to give 3-*tert*-butyloxycarbonylamino-4-thiophene amidoxime **39** (3.47 g, 100%) as a solid.  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  10.15 (1H, s), 9.85 (1H, s), 7.90 (1H, s), 7.51 (1H, s), 6.05 (2H, s), 1.47 (9H, s).

10



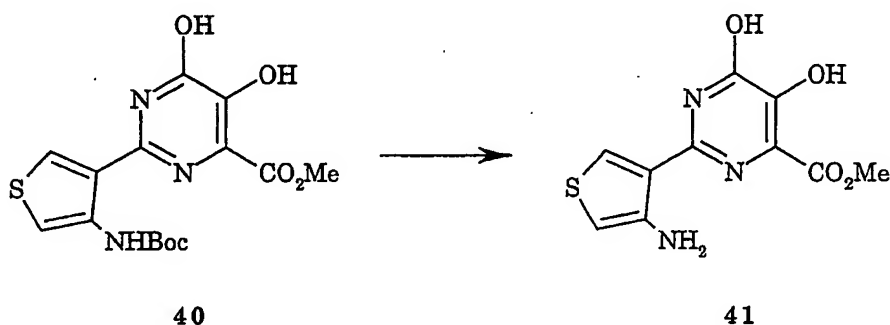
15

Dimethyl acetylenedicarboxylate (1.84 g, 13 mmol) was added dropwise to a stirred solution of oxime **39** (3.27 g, 12.7 mmol). The mixture was treated with triethylamine (0.25 ml) and heated under reflux for 3 h. The cooled solution was concentrated *in vacuo* and the residue was filtered through a short path of  $\text{SiO}_2$  (3:1 petroleum ether:ethyl

20

acetate as eluent) to give a solid which was taken up in *p*-xylene (100 ml). The solution was heated under reflux for 3.5 h and then cooled and filtered. The precipitate was washed with methanol (5 ml) and diethyl ether (20 ml) and dried to give methyl 2-(3-*tert*-butoxycarbonylamino-4-thienyl)-4,5-dihydroxypyrimidine-6-carboxylate **40** (1.3 g, 28%) as a solid.

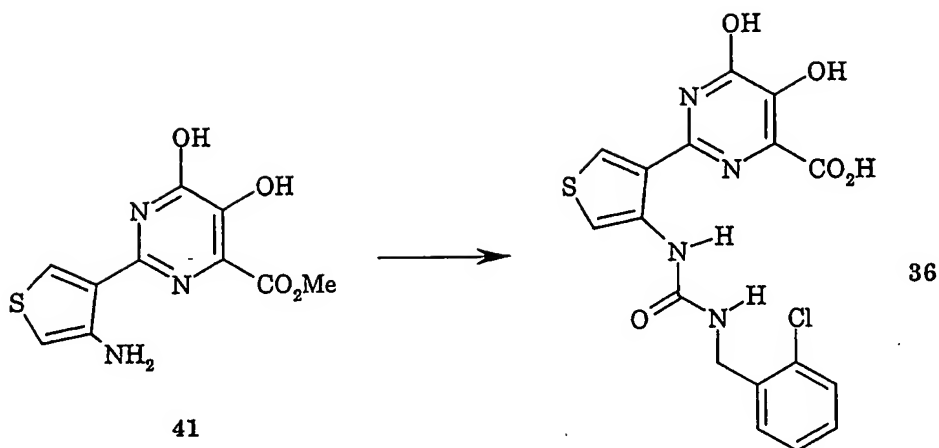
5 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 13.10 (1H, bs), 10.90 (1H, s), 10.78 (1H, bs), 8.49 (1H, s), 7.70 (1H, s), 3.85 (3H, s), 1.48 (9H, s).



10

Ester **40** (828 mg, 2.25 mmol), prepared as described above, was treated with a 6:4 mixture of methylene chloride:trifluoroacetic acid (8 ml). The solution was stirred for 20 min then concentrated *in vacuo* and the residue dried to give methyl 2-(3-amino-4-thienyl)-4,5-dihydroxypyrimidine-6-carboxylate trifluoroacetate (860 mg, 99%) as a solid.

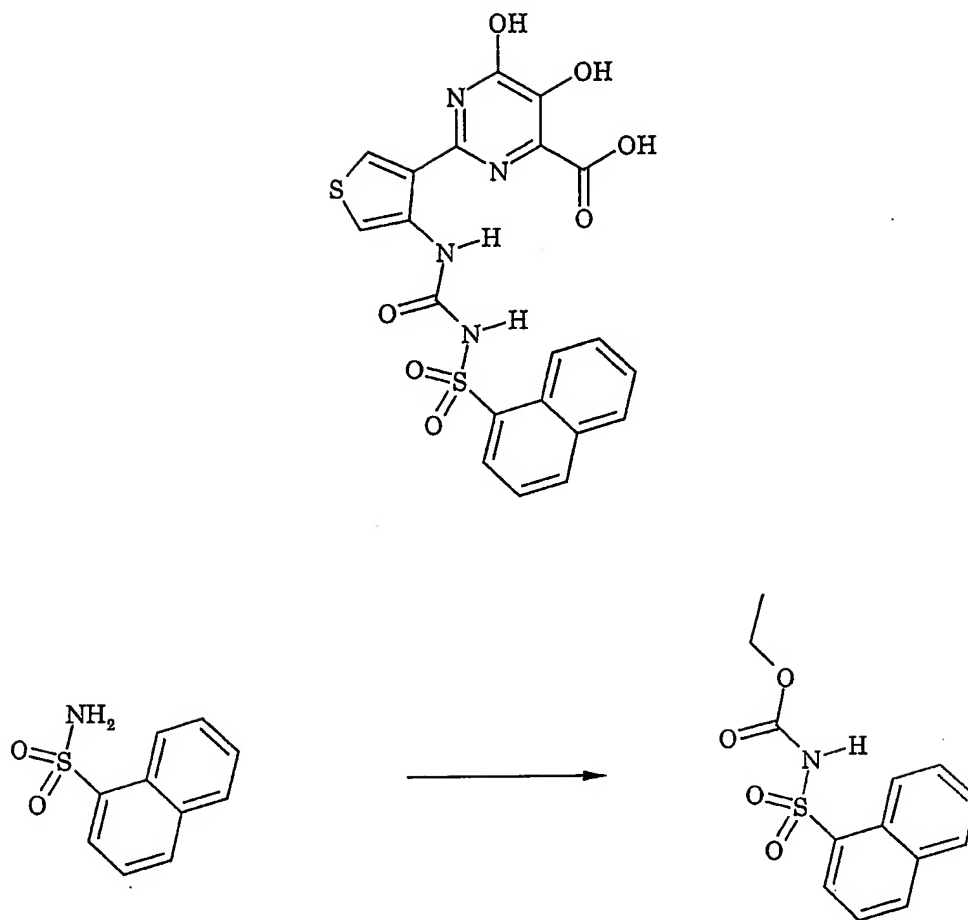
15 <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 8.32 (1H, s), 6.75 (1H, s), 3.87 (3H, s). MS *m/z* (MH)<sup>+</sup> 268.0.



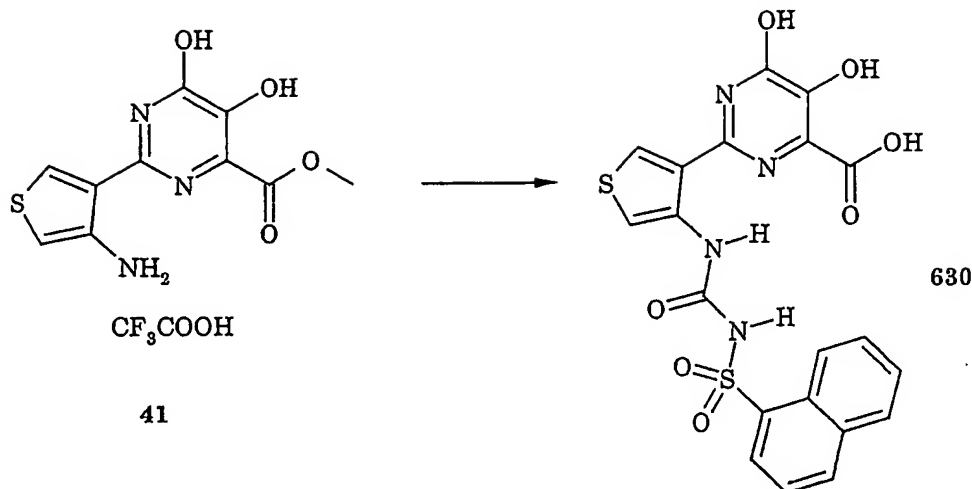
A solution of amine 41 (200 mg, 0.58 mmol) in pyridine (5 ml) was treated dropwise with 2-chlorobenzyl isocyanate and the mixture was stirred for 8 h. The solution was concentrated *in vacuo* and the residue was washed with 1N hydrochloric acid (2 ml), water (2 ml) and diethyl ether (2 ml) to give a solid (199 mg) which was taken up in 1N sodium hydroxide (2 ml). The mixture was heated at 60°C for 5.5 h then cooled to 0°C and acidified with 1N hydrochloric acid. The precipitate was collected and washed with water (5 ml) and diethyl ether (5 ml). Purification of a 40 mg portion by HPLC (MacheryNagel Nucleosil C<sub>18</sub> 25 mm x 20 cm; eluent MeCN + 0.1% TFA/H<sub>2</sub>O + 0.1% TFA; gradient from 30% MeCN to 90% MeCN in 10 min; retention time = 8 min) afforded the title compound (12 mg) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.80 (1H, bs), 11.60 (1H, s), 8.35 (d, *J* 4), 7.61 (1H, d, *J* 4), 7.43 (2H, m), 7.32 (2H, m), 6.52 (1H, t, *J* 4.8), 4.41 (2H, d, *J* 4.8). MS *m/z* (M<sup>+</sup>) 419.0.

### EXAMPLE 8

5,6-Dihydroxy-2-[4-(1-naphthylsulfonylaminocarbonylamino)thien-3-yl]pyrimidine-4-carboxylic acid (630)

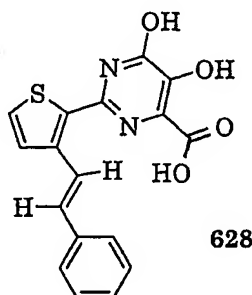


A mixture of 1-naphthalene sulfonamide (769 mg, 3.67 mmol) and  
5 potassium carbonate (563 mg, 4.07 mmol) in 2-butanone (9 ml) was heated  
under reflux for 30 min. Ethyl chloroformate (430 mg, 3.96 mmol) was  
added dropwise and the resulting solution was heated under reflux for 3 h.  
The mixture was cooled and diluted with H<sub>2</sub>O (30 ml) and AcOEt (10 ml).  
The aqueous layer was collected and adjusted to pH 2 by addition of 1N  
10 HCl (aq). Extraction with AcOEt (2 x 20 ml) and concentration of the  
dried organic extracts afforded ethyl 1-naphthylsulfonylcarbamate (674  
mg, 67%) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.35 (bs, 1H), 8.57 (1H,  
d, *J* 8.6), 8.29 (2H, m), 8.11 (1H, d, *J* 7.7), 7.71 (3H, m), 3.90 (2H, q, *J* 7.1),  
0.99 (3H, t, *J* 7.1).



A solution of amine 41 (200 mg, 0.52 mmol) in toluene (4 ml) was treated with triethylamine (99 mg, 0.98 mmol) to adjust the pH to 6. Ethyl 1-naphthylsulfonylcarbamate (137 mg, 0.49 mmol) was added and the mixture was heated to reflux for 30 min. The mixture was cooled to room temperature and treated with 1N HCl (aq). The precipitate was filtered and triturated with H<sub>2</sub>O and Et<sub>2</sub>O then dried to afford methyl 5,6-dihydroxy-2-[4-(1-naphthylsulfonylaminocarbonylamino)thien-3-yl]pyrimidine-4-carboxylate (224 mg, 86%) as a solid. A portion of this compound (109 mg, 0.22 mmol) was dissolved in a 4:1 mixture of THF/H<sub>2</sub>O (2.2 ml) and was treated with LiOH.H<sub>2</sub>O (46 mg, 1.09 mmol). The mixture was heated overnight at 50°C, then the solution was cooled and the THF was removed under vacuum. The residue was acidified to pH 2 with 1N HCl (aq) and the resulting precipitate was collected by filtration, triturated with H<sub>2</sub>O and Et<sub>2</sub>O, and dried to afford the title compound (101 mg, 94%) as a solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.90 (1H, bs), 11.30 (1H, bs), 8.63 (1H, d, *J* 8.5), 8.28 (3H, m), 8.09 (1H, d, *J* 8), 7.69 (3H, m), 7.45 (1H, d, *J* 3.3); MS (ESI) 485 [M-H].



**EXAMPLE 9****5,6-Dihydroxy-2-{3-[(*E*)-2-phenylethenyl]thien-2-yl}pyrimidine-4-carboxylic acid (628)**

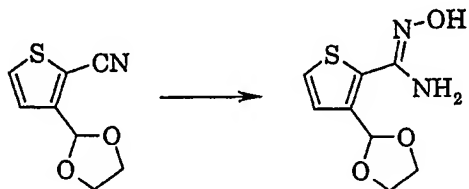
5



3-(1,3-Dioxolan-2-yl)thiophene-2-carbaldehyde (13.1 g, 71.11 mmol), prepared by a method described by Hibino (S. Hibino *et al.*, *J. Org. Chem.* 1984, 49, 5006), was dissolved in ethanol (80 ml). At room temperature a solution of hydroxylamine hydrochloride (two equivalents) and sodium hydrogencarbonate (one equivalent) in water (130 ml) was added and the resultant mixture stirred at this temperature for two hours. The ethanol was removed under reduced pressure and the aqueous phase extracted with ethyl acetate (3 x 300 ml). The combined organic layers were washed with brine and dried over sodium sulfate. Evaporation after filtration afforded 3-(1,3-dioxolan-2-yl)thiophene-2-carbaldehyde oxime as an off-white solid (quantitative). <sup>1</sup>H NMR (2 isomers, 1:1) (CDCl<sub>3</sub>): δ 8.56 (1H, s), 8.45 (1H, s), 7.50 (1H, d, *J* 5.26), 7.25 (1H, d, *J* 5.2), 7.21 (1H, d, *J* 5.28), 7.12 (1H, d, *J* 5.2), 6.09 (1H, s), 5.99 (1H, s), 4.17-4.00 (2H, m).

The foregoing aldoxime (10.09 g, 50.07 mmol) was dissolved in acetonitrile (139 ml) containing copper(II) acetate hydrate (1.01 g, 5.07 mmol). Triethylamine (19.6 ml) was added dropwise and the resulting mixture was heated to reflux. After 30 min TLC (hexanes/ethyl acetate

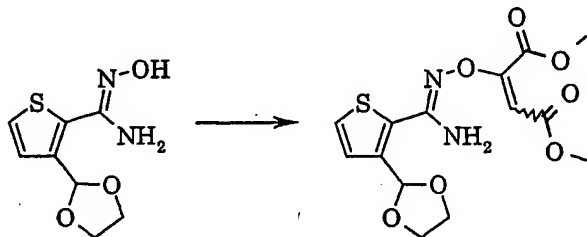
3:1) indicated complete conversion of starting material. After cooling the reaction mixture to room temperature, the solvents were evaporated under reduced pressure and the crude product was purified by flash chromatography (eluent hexanes/ethyl acetate 3:1) to give 7.78 g (87%) of 3-(1,3-dioxolan-2-yl)thiophene-2-carbonitrile as an oily liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.55 (1H, d, *J* 5.20), 7.21 (1H, d, *J* 5.20), 6.04 (1H, s), 4.21-4.06 (4H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 149.69, 131.89, 126.79, 112.83, 108.22, 98.60, 65.52.



10

To a solution of the foregoing nitrile (5.0 g, 27.59 mmol) in ethanol (20 ml) was added a solution of hydroxylamine hydrochloride (3.7 equivalents) and sodium carbonate (1.7 equivalents) in water (50 ml). The resulting mixture was heated to 40°C for 5 h, then cooled to room temperature. The colourless precipitate was isolated by filtration, dried under a stream of air and azeotroped with toluene (2 x) to give 3-(1,3-dioxolan-2-yl)thiophene-2-amidoxime as an off-white solid (4.36 g). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 9.83 (1H, s), 7.48 (1H, d, *J* 5.18), 7.15 (1H, d, *J* 5.18), 6.05 (1H, s), 5.77 (2H, bs), 4.05 (2H, m), 3.91 (2H, m).

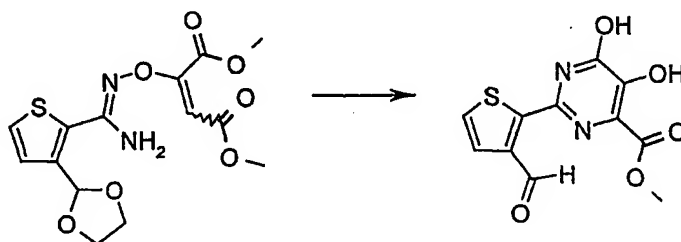
20



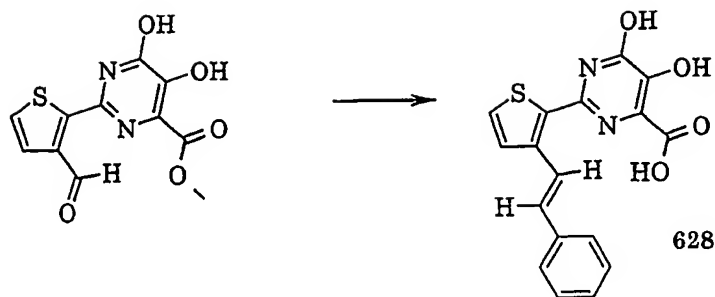
The foregoing compound (4.35 g, 20.3 mmol) was suspended in dichloromethane (200 ml). Triethylamine (0.2 ml) and dimethyl acetylenedicarboxylate (2.89 g, 20.3 mmol) were added. The mixture was refluxed

for 5 h, then another portion of dimethyl acetylenedicarboxylate (289 mg) was added and the mixture was left stirring at room temperature for 3 days. Evaporation gave a red oil, which was purified by flash

- 5 The product was obtained as a yellow oil (6.38 g, two diastereomers 1.5:1\*).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.67\*, 7.64 (1H, d,  $J$  5.17), 7.19\*, 7.16 (1H, d,  $J$  5.17), 7.08\*, 6.70 (2H, bs), 6.02\*, 5.99 (1H, s), 5.73, 5.69\* (1H, s), 4.04 (2H, m), 3.93 (2H, m), 3.80\*, 3.77 (3H, s), 3.62, 3.61\* (3H, s). MS  $m/z$  ( $\text{MH}^+$ ) 357.



- 10 The foregoing compound (6.29 g, 17.65 mmol) was heated at reflux in xylene (120 ml) for 6 h and then cooled to room temperature. The reaction was filtered to remove some black precipitate and the solution cooled to 0°C. An orange solid precipitated, which was collected by filtration. The solution was reduced to half of its volume under reduced
- 15 pressure and the precipitate that formed upon cooling to 0°C was collected and united with the first batch. Thus, 2.0 g of cyclized material was obtained. A portion of this material (512 mg) was heated to 50°C in formic acid (50 ml) for 1 h. The formic acid was removed under reduced pressure and the remaining solid was azeotroped with toluene (2 x) to obtain crude
- 20 methyl 2-(3-formylthien-2-yl)-5,6-dihydroxypyrimidine-4-carboxylate (452 mg). This material was used without further purification.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ):  $\delta$  9.83 (1H, s), 7.48 (1H, d,  $J$  5.18), 7.15 (1H, d,  $J$  5.18), 6.05 (1H, s), 5.77 (2H, bs), 4.05 (2H, m), 3.91 (2H, m). MS  $m/z$  ( $\text{M}+\text{H}$ ) 281.



The crude foregoing product (80 mg, 0.29 mmol) was dissolved in methanol (1 ml) and *N,N*-dimethylformamide (2 ml) and treated with sodium methanolate (2 equivalents). The resulting red solution was added to a solution of benzyl triphenylphosphonium bromide (247 mg, 2 equivalents) and sodium methanolate (34 mg) in anhydrous methanol (5 ml), which was prepared 20 min before at room temperature. The resulting mixture was heated to reflux. After 4 h some of the methanol was evaporated under reduced pressure, ethyl acetate was added, and the solution was washed with hydrochloric acid (1N) and brine. After drying over sodium sulfate, filtration and evaporation under reduced pressure, an orange solid was obtained, which was treated with diethyl ether (5 x 7 ml). The remaining solid (60 mg) was dissolved in methanol (1 ml) and sodium hydroxide (1 ml, 0.5N) was added. After heating to 80°C for 1 h, the reaction mixture was diluted with water, and then at room temperature hydrochloric acid (1N) was added dropwise until pH 2 was reached. The precipitate was isolated by filtration, washed with diethyl ether and then lyophilized from acetonitrile and water. 5,6-Dihydroxy-2-{3-[(*E*)-2-phenylethenyl]thien-2-yl}pyrimidine-4-carboxylic acid was obtained as a yellow powder (35 mg). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 13.00 (1H, bs), 8.03 (1H, bd, *J* 16.9), 7.71 (1H, d, *J* 5.2), 7.63 (1H, d, *J* 5.2), 7.59 (2H, d, *J* 7.5), 7.36 (2H, t, *J* 7.5), 7.27 (1H, d, *J* 7.7), 7.23 (1H, d, *J* 16.9). MS *m/z* 341 (M+H)<sup>+</sup>.

These and other compounds of the invention which can be prepared by analogous methods are set out in Tables I to XII below. Where "X<sub>1</sub>" appears in the Table it is not part of the group "R<sub>1</sub>" but represents the

remainder of the molecule apart from R1. The IC<sub>50</sub> values in µM of these compounds can be measured in the following way.

Test for Inhibition of Hepatitis C Virus RdRp

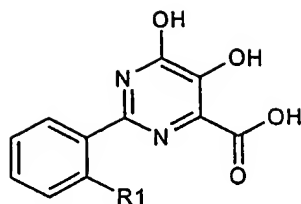
5 WO 96/37619 describes the production of recombinant HCV RdRp from insect cells infected with recombinant baculovirus encoding the enzyme. The purified enzyme was shown to possess *in vitro* RNA polymerase activity using RNA as template. The reference describes a polymerisation assay using poly(A) as a template and oligo(U) as a primer.  
10 Incorporation of tritiated UTP is quantified by measuring acid-insoluble radioactivity. The present inventors have employed this assay to screen the various compounds described above as inhibitors of HCV RdRp.

Incorporation of radioactive UMP was measured as follows. The standard reaction (100 µl) was carried out in a buffer containing 20 mM  
15 tris/HCl pH 7.5, 5 mM MgCl<sub>2</sub>, 1 mM DTT, 50 mM NaCl, 1 mM EDTA, 20U Rnasin (Promega), 0.05% Triton X-100, 1 µCi [<sup>3</sup>H]-UTP (40 Ci/mmol, NEN), 10 µM UTP and 10 µg/ml poly(A). Oligo(U)<sub>12</sub> (1 µg/ml, Genset) was added as a primer. The final NSSB enzyme concentration was 20 nM. After 1 h incubation at 22°C the reaction was stopped by adding 100 µl of  
20 20% TCA and applying samples to DE81 filters. The filters were washed thoroughly with 5% TCA containing 1M Na<sub>2</sub>HPO<sub>4</sub>/NaH<sub>2</sub>PO<sub>4</sub>, pH 7.0, rinsed with water and then ethanol, air dried, and the filter-bound radioactivity was measured in the scintillation counter. By carrying out the reaction in the presence of various concentrations of each of the  
25 compounds set out above it was possible to determine IC<sub>50</sub> values for each compound utilizing the formula:

$$\% \text{ residual activity} = 100 / (1 + [I] / IC_{50})^s$$

30 where [I] is the inhibitor concentration and "s" is the slope of the inhibition curve.

Table I



Ex. No.	R1
4 (Compound No. 21)	<p>Chemical structure of R1 for Example 4: A 2,4,6-trichlorophenyl group with a sulfonamide group (-SO<sub>2</sub>NH-X<sub>1</sub>) at position 1.</p>
42	<p>Chemical structure of R1 for Example 42: A 2,4,6-trichlorophenyl group with a sulfonamide group (-SO<sub>2</sub>NH-X<sub>1</sub>) at position 1.</p>
43	<p>Chemical structure of R1 for Example 43: A 2-chloro-3-methylbenzyl group with a carbamate group (-NHCO-NH-X<sub>1</sub>) at the benzylic position.</p>
2 (Compound No. 9)	<p>Chemical structure of R1 for Example 2: A 2-chlorobenzyl group with a carbamate group (-NHCO-NH-X<sub>1</sub>) at the benzylic position.</p>
44	<p>Chemical structure of R1 for Example 44: A 2-bromobenzyl group with a carbamate group (-NHCO-NH-X<sub>1</sub>) at the benzylic position.</p>
45	<p>Chemical structure of R1 for Example 45: A 2,4-dichloro-3-methylphenyl group with a sulfonamide group (-SO<sub>2</sub>NH-X<sub>1</sub>) at position 1.</p>

Table I

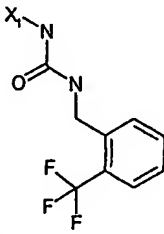
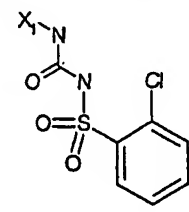
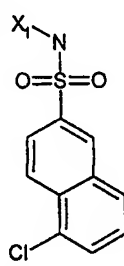
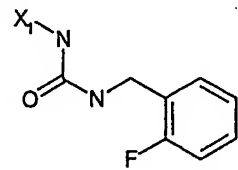
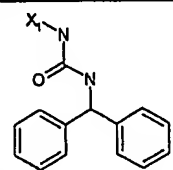
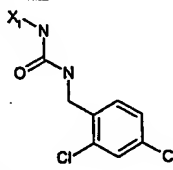
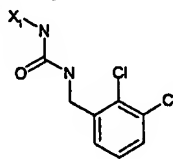
46	
47	
48	
49	
50	
51	
52	

Table I

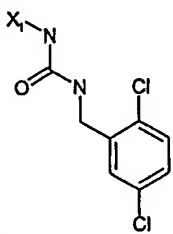
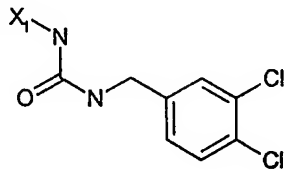
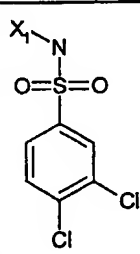
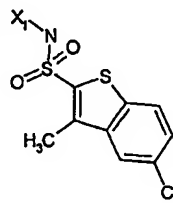
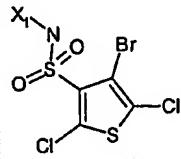
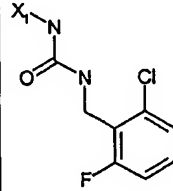
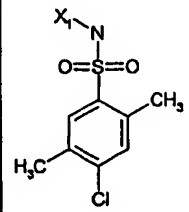
53	
54	
55	
56	
57	
58	
59	



Table I

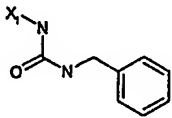
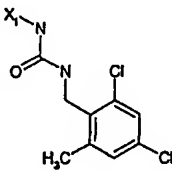
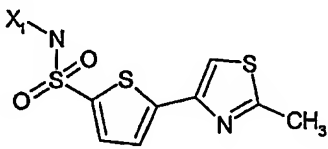
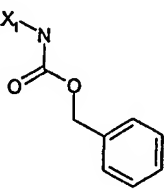
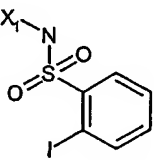
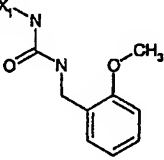
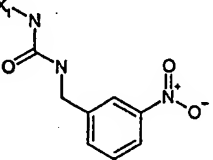
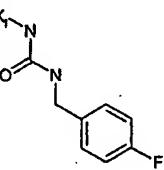
60	
61	
62	
63	
64	
65	
66	
67	

Table I

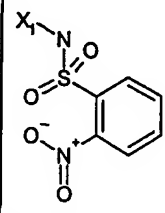
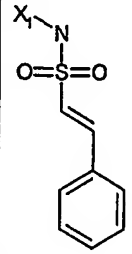
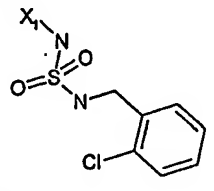
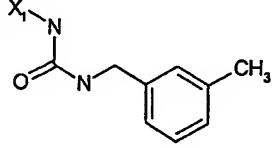
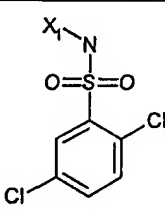
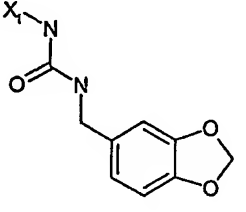
68	
69	
70	
71	
72	
73	

Table I

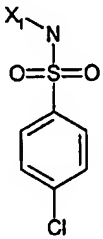
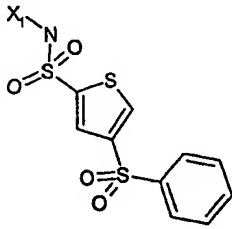
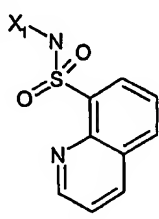
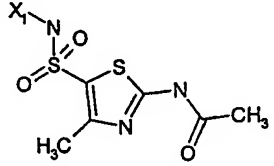
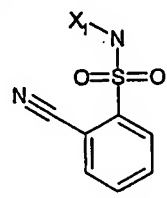
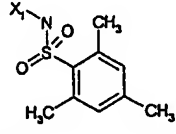
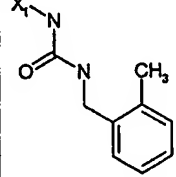
74	
75	
76	
77	
78	
79	
80	

Table I

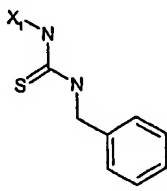
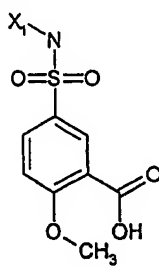
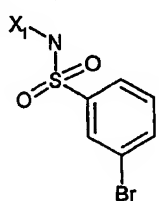
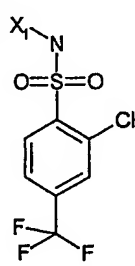
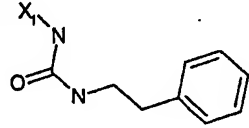
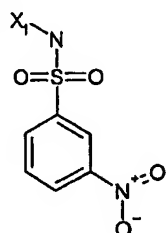
81	
82	
83	
84	
85	
86	

Table I

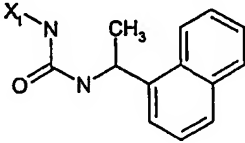
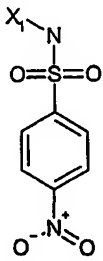
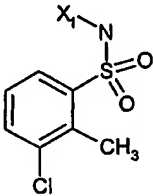
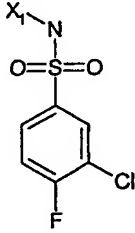
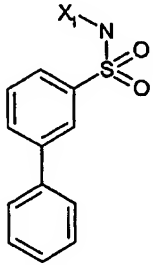
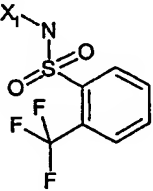
87	
88	
89	
90	
91	
92	

Table I

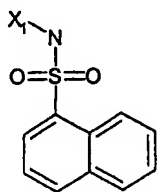
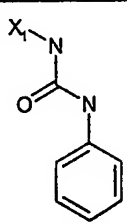
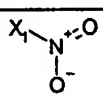
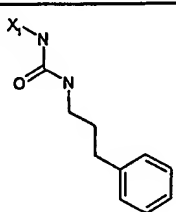
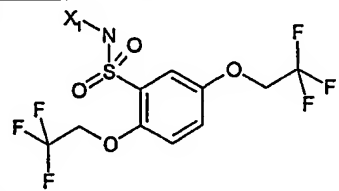
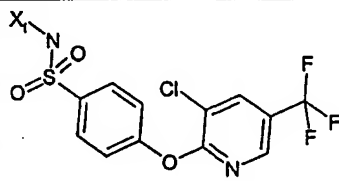
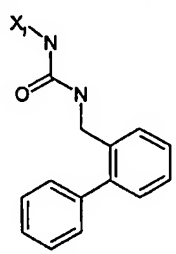
93	
94	
95	
96	
97	
98	
99	

Table I

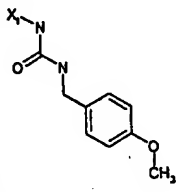
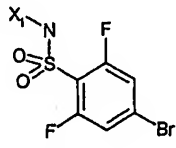
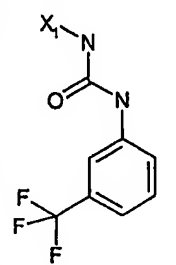
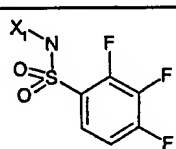
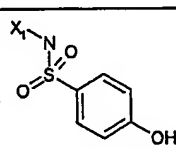
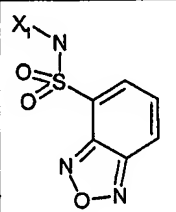
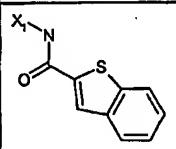
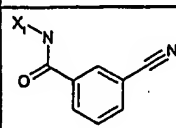
100	
101	
102	
103	
104	
105	
106	
107	

Table I

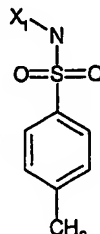
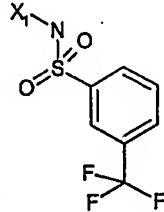
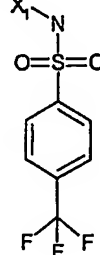
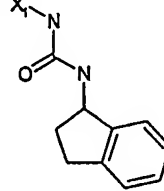
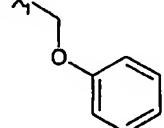
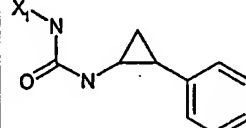
108	
109	
110	
111	
112	
113	



Table I

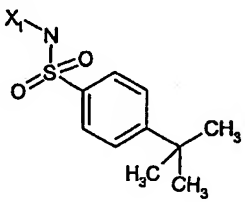
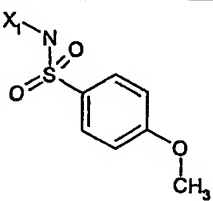
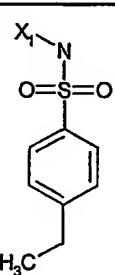
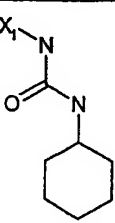
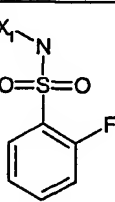
114	
115	
116	
117	
118	$X_1\text{-Br}$
119	
120	$X_1\text{-OH}$
121	$X_1\text{-Cl}$

Table I

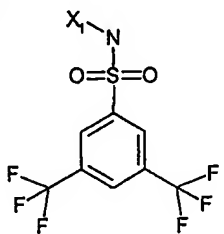
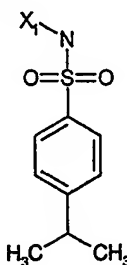
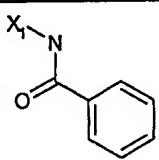
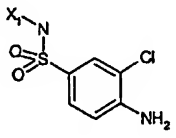
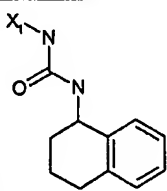
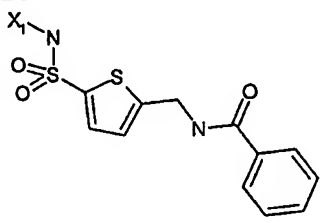
122	
123	
124	
125	
126	$X_1-NH_2$
127	
128	
129	$X_1-H$

Table I

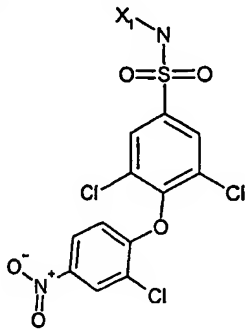
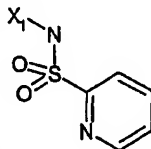
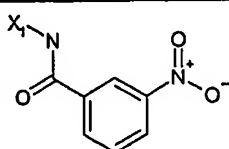
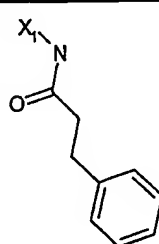
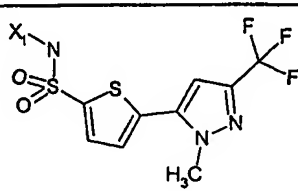
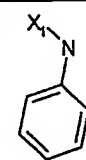
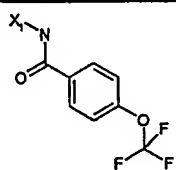
130	
131	
132	
133	
134	
135	
136	

Table I

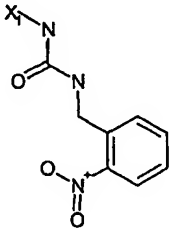
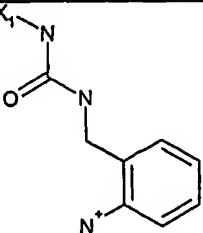
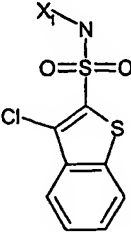
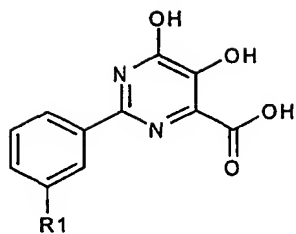
594	
595	
596	

Table II



Ex. No.	R1
137	
138	
139	
140	
3 (Compound No. 15)	

Table II

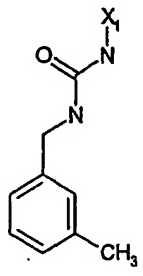
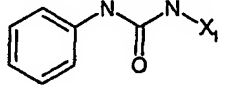
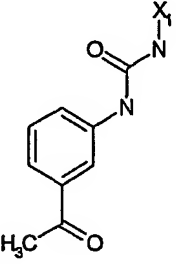
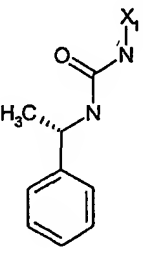
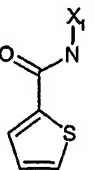
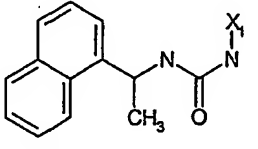
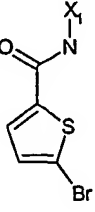
141	
142	
143	
144	
145	
146	
147	

Table II

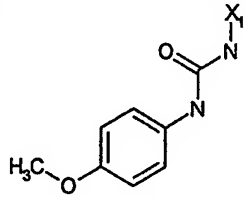
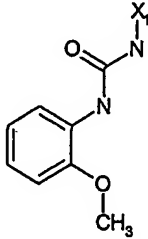
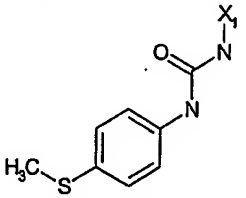
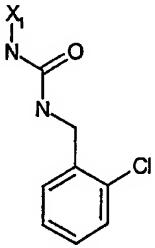
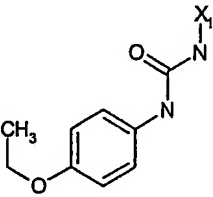
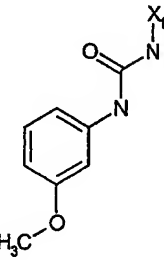
148	
149	
150	
151	
152	
153	

Table II

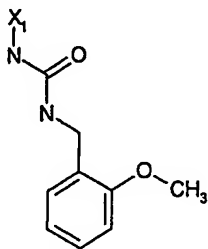
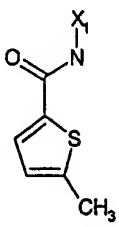
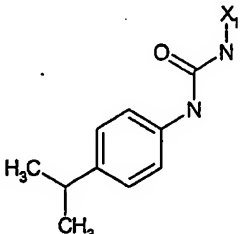
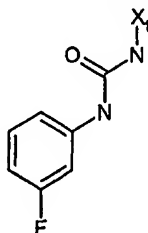
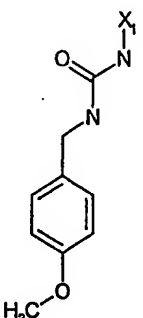
154	
155	
156	
157	
158	



Table II

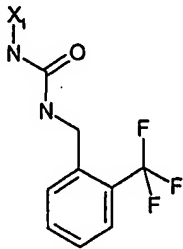
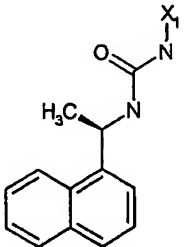
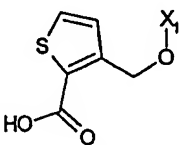
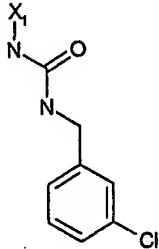
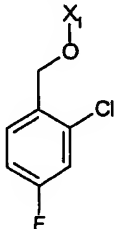
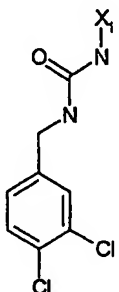
159	
160	
161	
162	
163	
164	

Table II

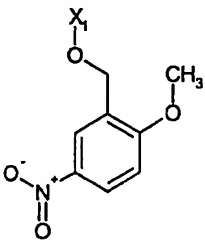
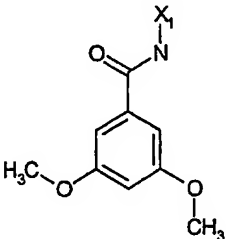
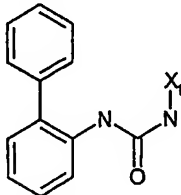
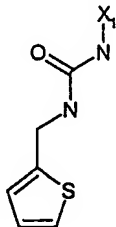
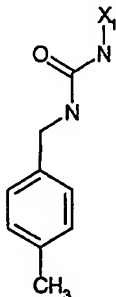
165	
166	
167	
168	
169	

Table II

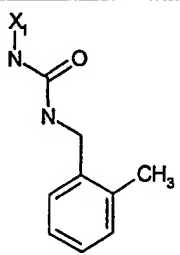
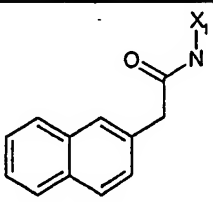
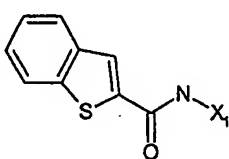
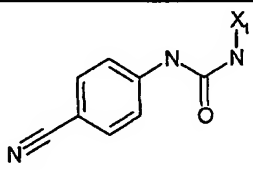
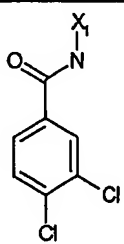
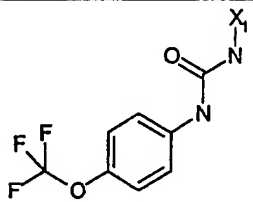
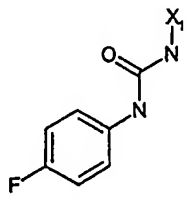
170	
171	
172	
173	
174	
175	
176	

Table II

177	
178	
179	
180	
181	
182	

Table II

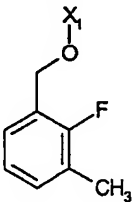

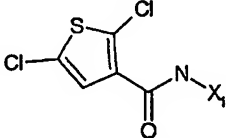
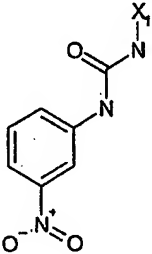
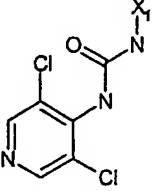
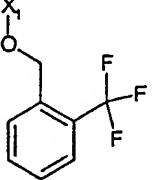
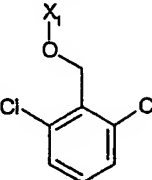
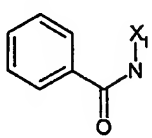
183	
184	
185	
186	
187	
188	
189	
190	

Table II

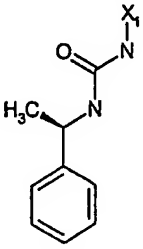
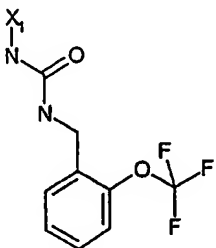
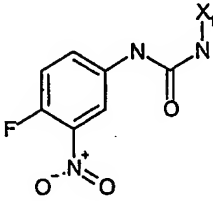
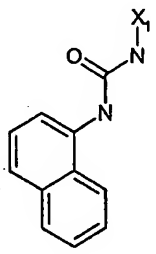
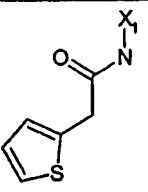
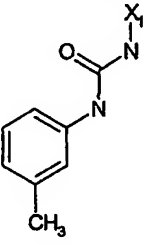
191	
192	
193	
194	
195	
196	

Table II

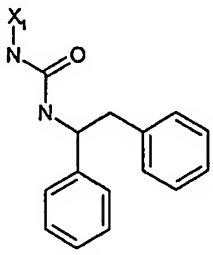
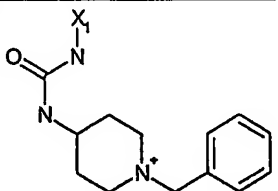
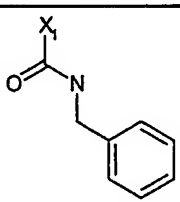
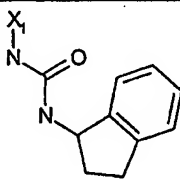
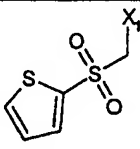
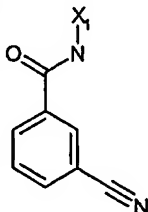
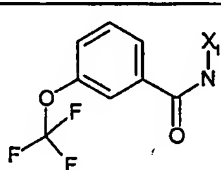
197	
198	
199	
200	
201	
202	
203	

Table II

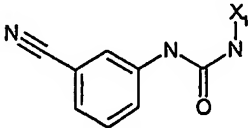
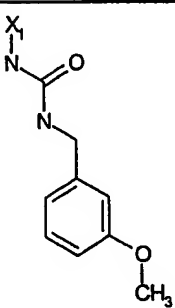
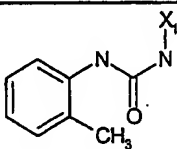
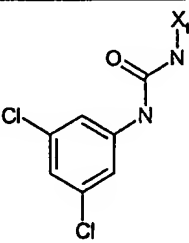
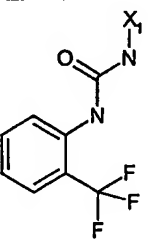
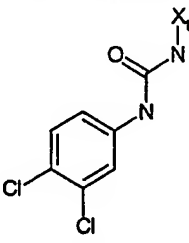
204	
205	
206	
207	
208	
209	



Table II

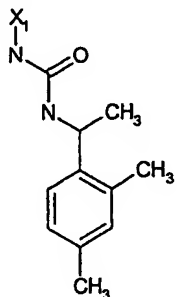
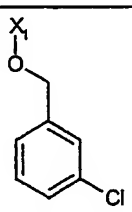
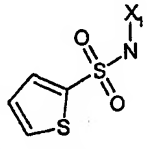

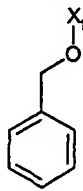
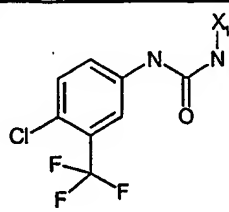
210	
211	
212	
213	
214	
215	

Table II

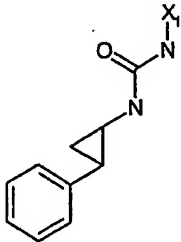
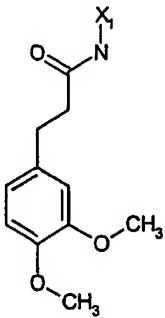
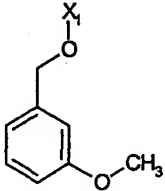
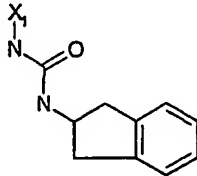

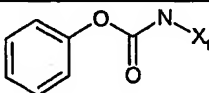
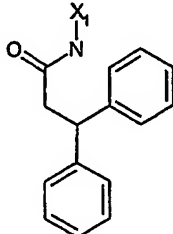

216	 <chem>N#CC(=O)NCC1CC1Cc2ccccc2</chem>
217	 <chem>CC(=O)NCCc1cc(OC)c(OC)cc1</chem>
218	 <chem>CC(=O)NCCc1cccc(OC)c1</chem>
219	 <chem>CC(=O)Nc1c2ccccc2CC1Cc3ccccc31</chem>
220	 <chem>CC(=O)N</chem>
221	 <chem>CC(=O)NOCc1ccccc1</chem>
222	 <chem>CC(=O)NCC(c1ccccc1)(c2ccccc2)c3ccccc3</chem>
223	 <chem>N</chem>

Table II


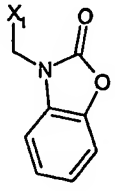
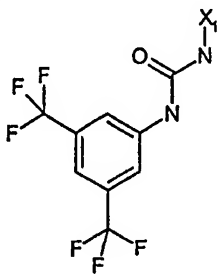
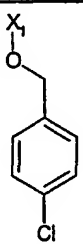
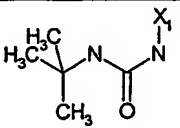
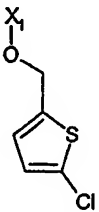
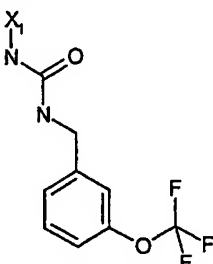
224	
225	
226	
227	
228	
229	
230	

Table II

231	
232	
233	
234	
235	
236	
237	
238	

Table II

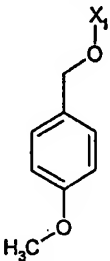
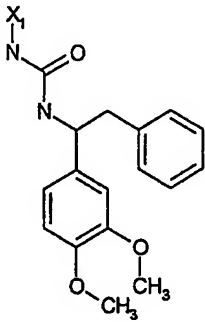
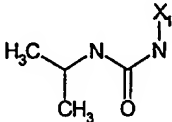
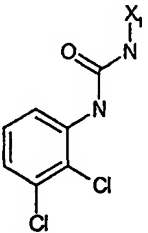
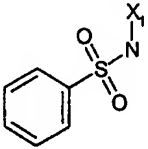
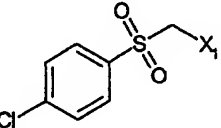
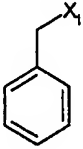
239	
240	
241	
242	
243	
244	
245	

Table II

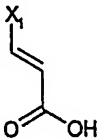

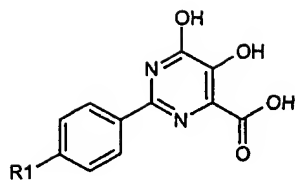
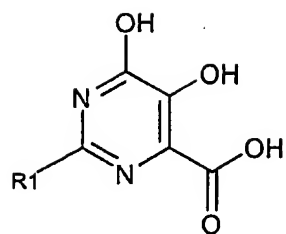
246	
247	

Table III



Ex. No.	R1
248	$\text{H}_3\text{C}-\text{X}_1$
249	$\text{Br}-\text{X}_1$
1 (Compound No. 7)	$\text{Cl}-\text{X}_1$
250	
251	
252	$\text{H}_2\text{N}-\text{X}_1$
253	

Table IV



Ex. No.	R1
254	<p>Chemical structure for R1 in Example 254. It consists of a 4-methyl-2-fluorophenyl group connected via a methylene group to an oxygen atom, which is part of a 4-hydroxyphenyl ring. The other substituent on this ring is <math>X_1</math>.</p>
255	<p>Chemical structure for R1 in Example 255. It features a thiophene ring connected via a carbonyl group to a nitrogen atom. This nitrogen is also bonded to a 2-(<math>X_1</math>)phenyl group and a sulfonamide group (<math>-SO_2-</math>) which is connected to a naphthalene ring.</p>
256	<p>Chemical structure for R1 in Example 256. It features a 4-chlorophenyl ring connected via a sulfonamide group (<math>-SO_2-</math>) to a naphthalene ring. The other substituent on the phenyl ring is <math>X_1</math>.</p>
257	<p>Chemical structure for R1 in Example 257. It features a 2-chloro-4-(<math>X_1</math>)phenyl ring connected via a nitrogen atom to a carbonyl group, which is further connected to a thiophene ring. The nitrogen is also bonded to a sulfonamide group (<math>-SO_2-</math>) which is connected to a naphthalene ring.</p>



Table IV

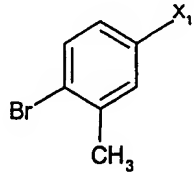
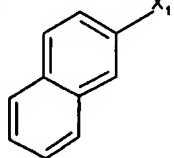
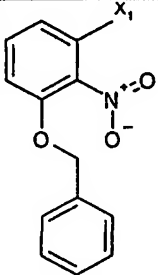
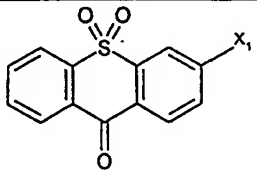
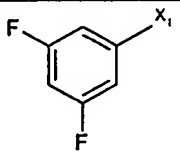
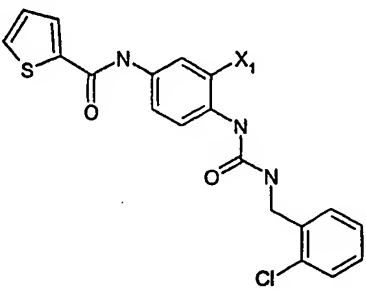
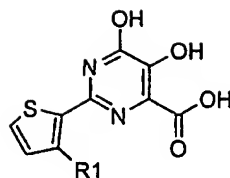
258	 <chem>Cc1cc(Br)cc(X1)c1</chem>
259	 <chem>c1ccc2ccccc2c1X1</chem>
260	 <chem>O=C1C=CC(=C(C=C1)OCc2ccccc2)[N+](=O)[O-]X1</chem>
261	 <chem>O=C1C(=O)c2cc(X1)ccc2S1(=O)=O</chem>
262	 <chem>Fc1cc(F)cc(X1)c1</chem>
597	 <chem>Clc1ccccc1N(C(=O)Nc2ccc(X1)cc2)C(=O)c3ccsc3</chem>

Table V



Ex. No.	
263	
264	
6 (Compound No. 27)	
265	
266	

Table V

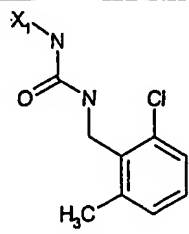
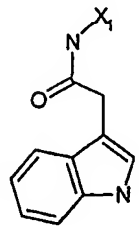
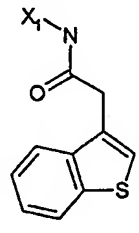
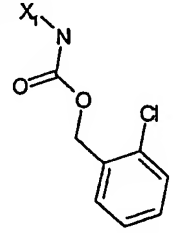
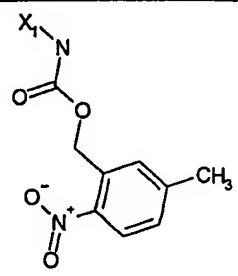
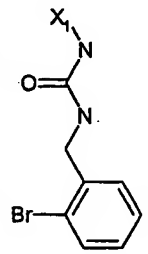
267	
268	
269	
270	
271	
272	

Table V

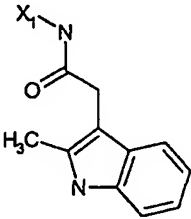
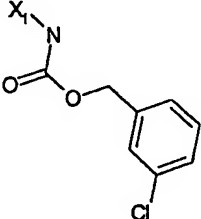
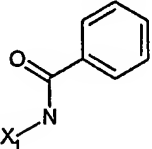
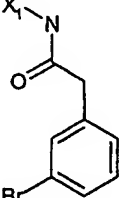
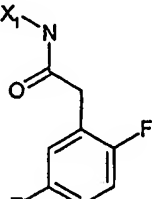
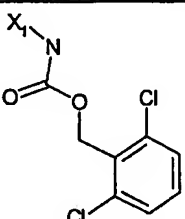
273	
274	
275	
276	
277	
278	

Table V

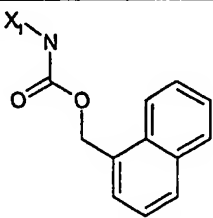
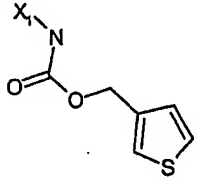
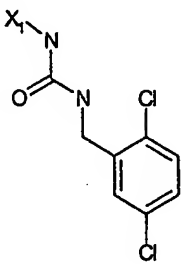
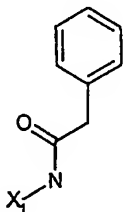
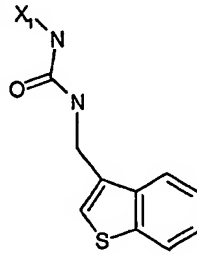
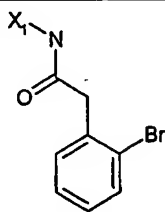
279	
280	
281	
282	
283	
284	

Table V

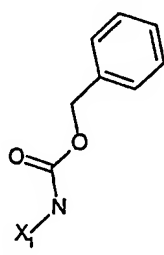
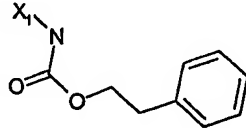
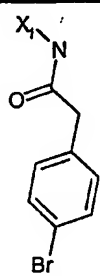
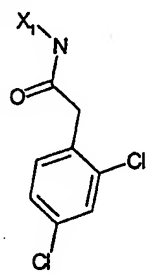
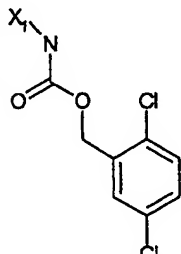
285	
286	
287	
288	
289	

Table V

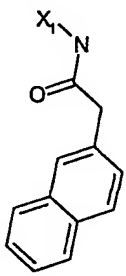
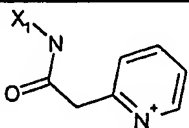
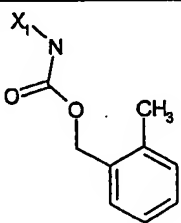
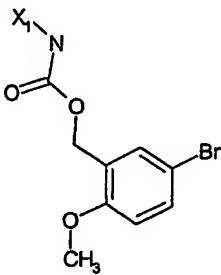
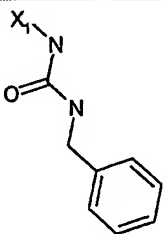
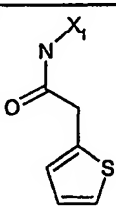
290	
291	
292	
293	
294	
295	

Table V

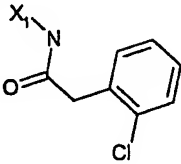
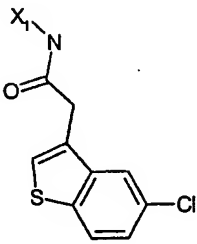
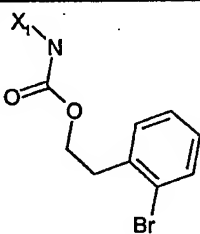
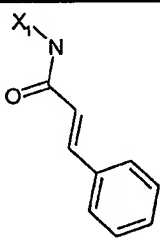

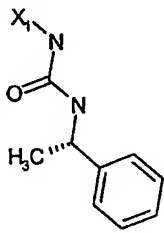
296	
297	
298	
299	
300	
301	



Table V

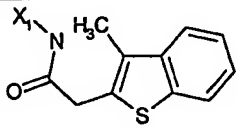
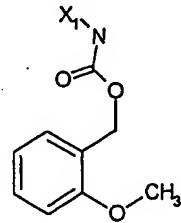
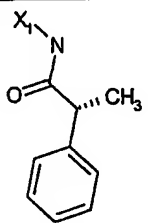
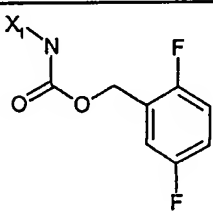
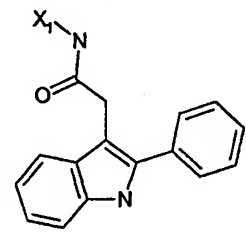
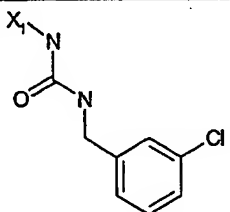
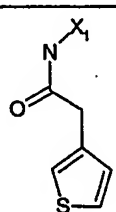
302	
303	
304	
305	
306	
307	
308	

Table V

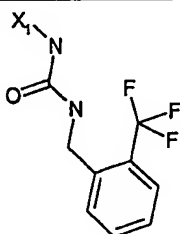
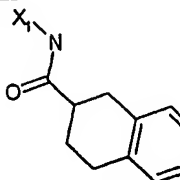
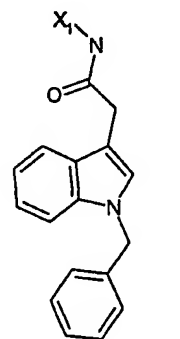
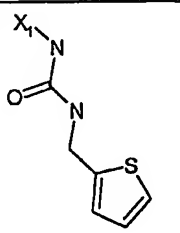
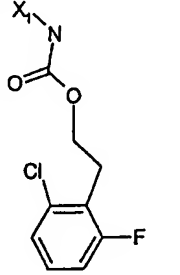
309	
310	
311	
312	
313	

Table V

314	
315	
316	
317	
318	
319	

Table V

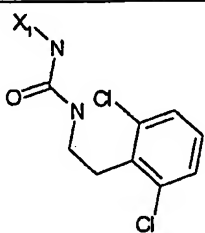
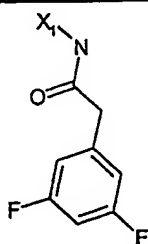
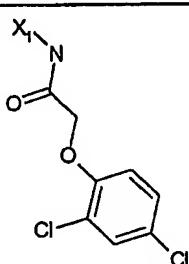
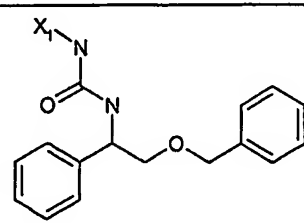
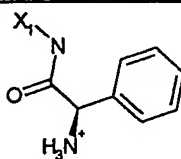
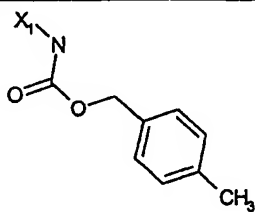
320	
321	
322	
323	
324	
325	

Table V

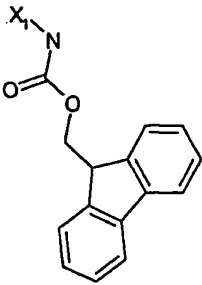
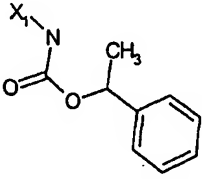
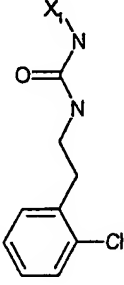
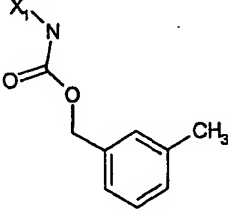
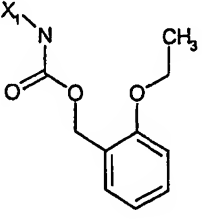
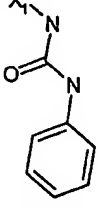
326	
327	
328	
329	
330	
331	

Table V

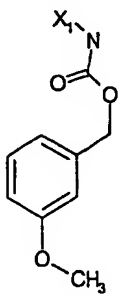
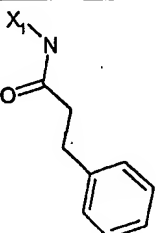
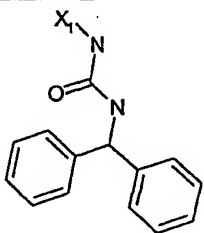
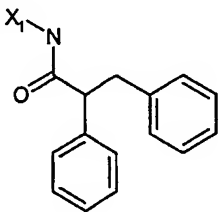
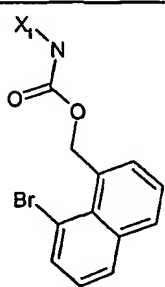
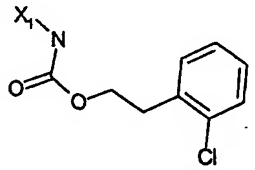
332	
333	
334	
335	
336	
337	

Table V

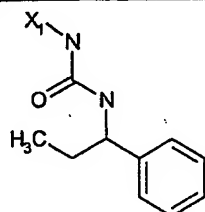
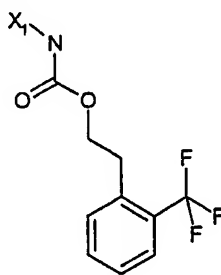
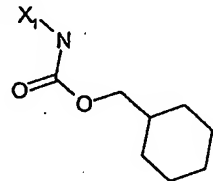
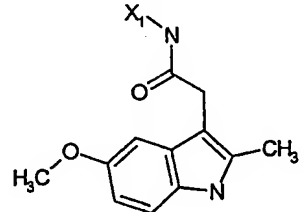
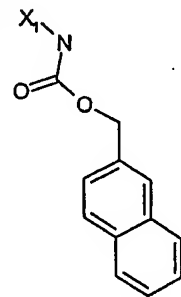
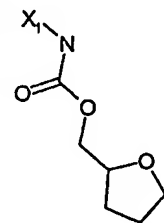
338	 <chem>CN1C(=O)N(C1Cc2ccccc2)C(=O)N</chem>
339	 <chem>CN1C(=O)N(C1Cc2ccccc2C(F)(F)F)C(=O)N</chem>
340	 <chem>CN1C(=O)N(C1CC2CCCCC2)C(=O)N</chem>
341	 <chem>CN1C(=O)N(C1Cc2c(C)cnc2OC)C(=O)N</chem>
342	 <chem>CN1C(=O)N(C1Cc2ccc3ccccc3c2)C(=O)N</chem>
343	 <chem>CN1C(=O)N(C1CC2OCC2)C(=O)N</chem>

Table V

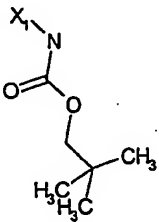
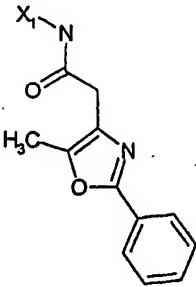
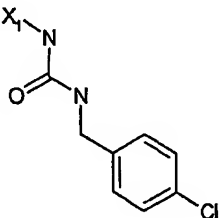
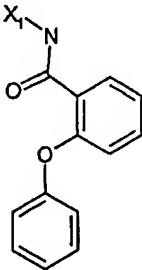
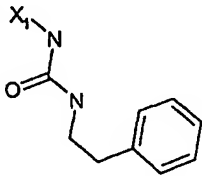
344	
345	
346	
347	
348	



Table V


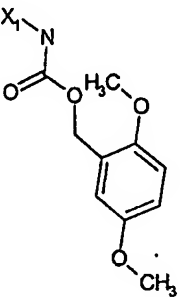
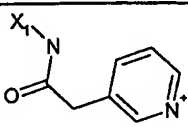
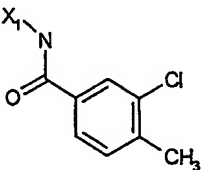
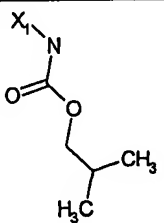
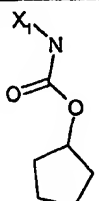
349	
350	
351	
352	
353	
354	

Table V

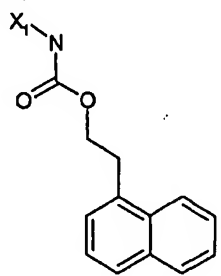
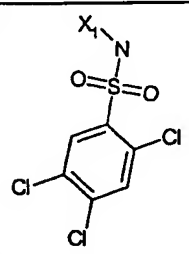
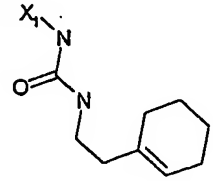
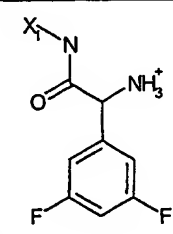
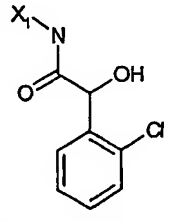
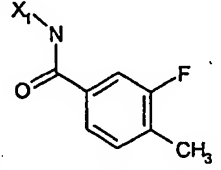
355	
356	
357	
358	
359	
360	

Table V

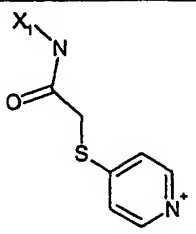
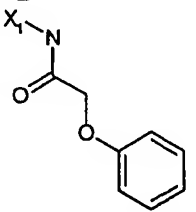
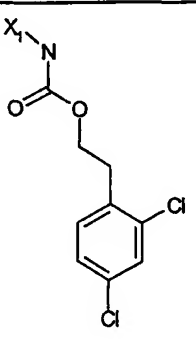
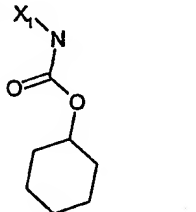
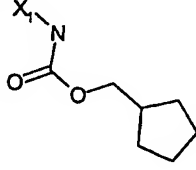
361	
362	
363	
364	
5 (Compound No. 24)	$X_1-H$
365	

Table V

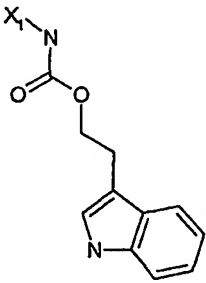
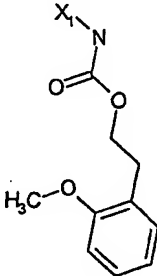
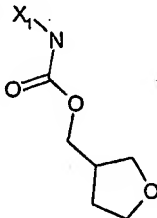
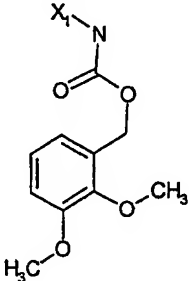
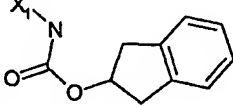
366	
367	
368	
369	
370	

Table V

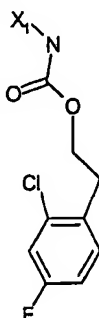
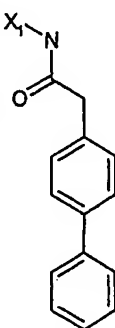
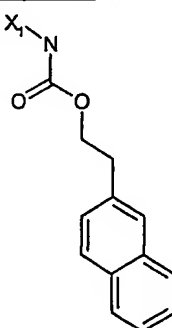
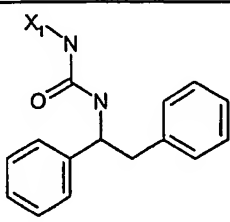
371	
372	
373	
374	

Table V

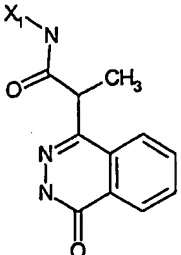
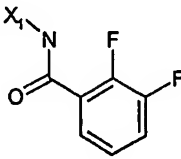
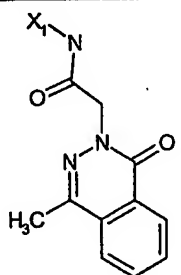
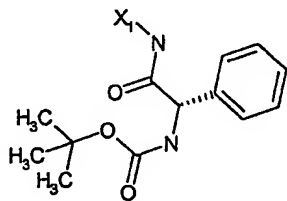
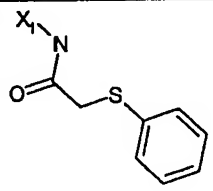
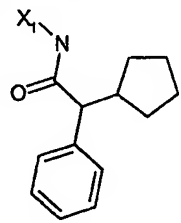
375	
376	
377	
378	
379	
380	

Table V

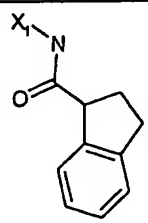
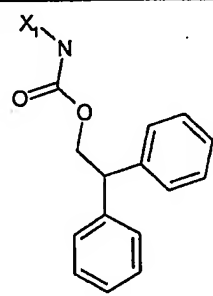
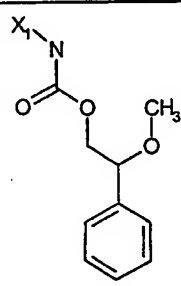
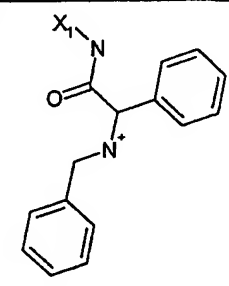
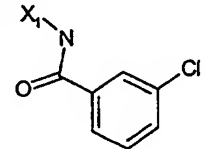
381	
382	
383	
384	
385	

Table V

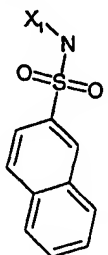
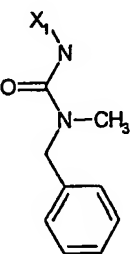
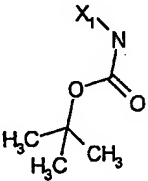
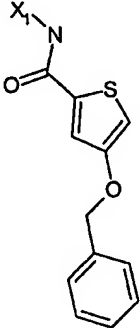
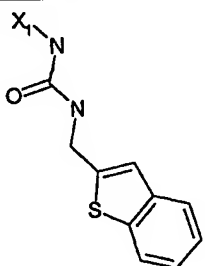
386	
387	
388	
389	
390	



Table V

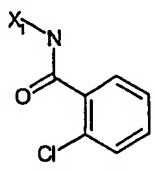

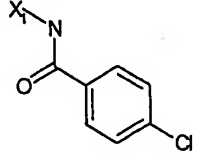
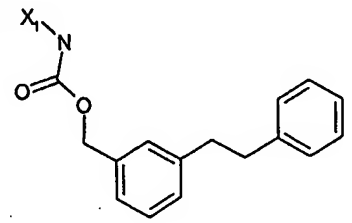
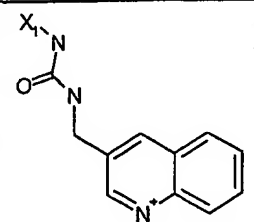
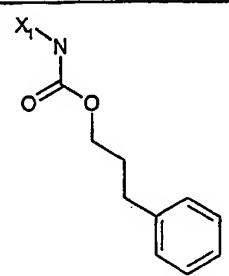
391	
392	
393	
394	
395	
396	

Table V

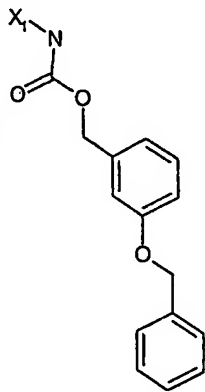
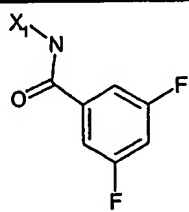
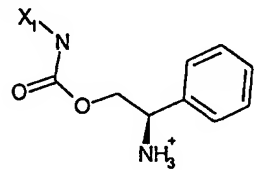
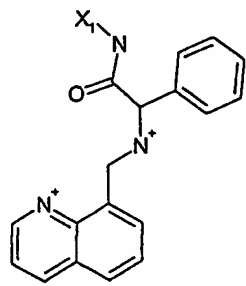
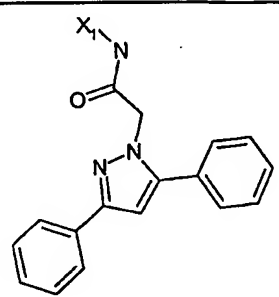
397	
398	
399	
400	
401	

Table V

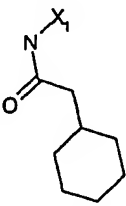
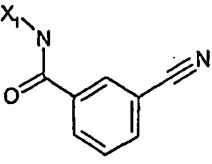
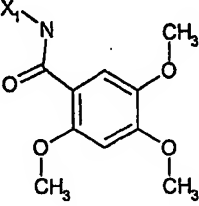
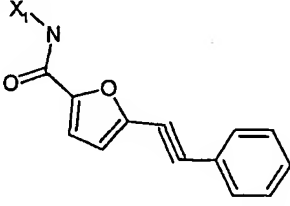
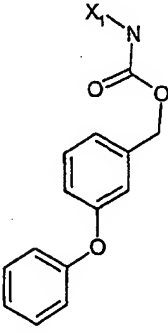
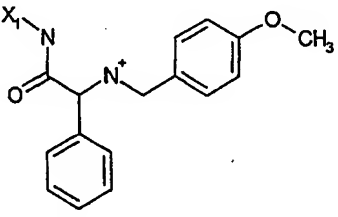
402	
403	
404	
405	
406	
407	

Table V

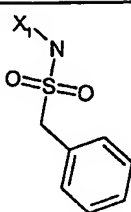
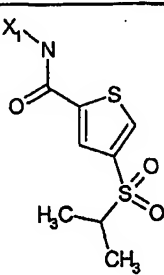

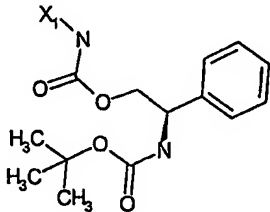
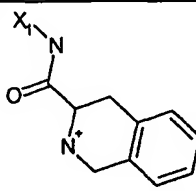
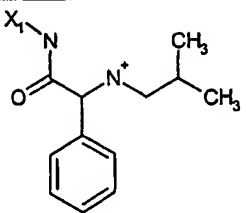
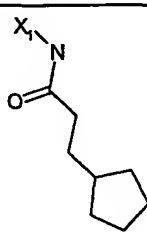
408	
409	
410	
411	
412	
413	
414	

Table V

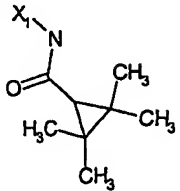
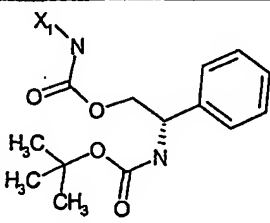
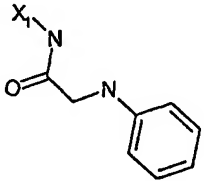
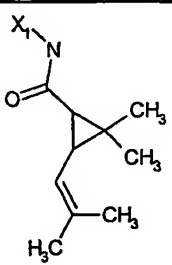
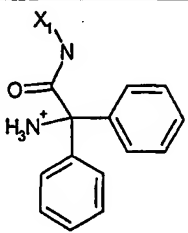
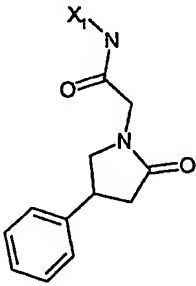
415	
416	
417	
418	
419	
420	

Table V

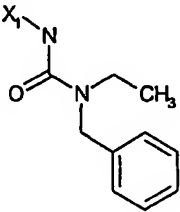
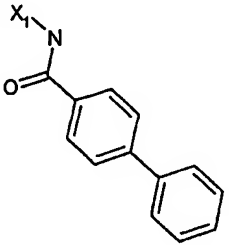
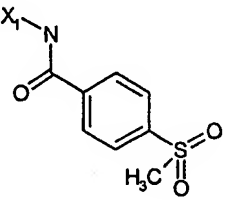
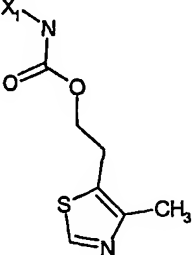
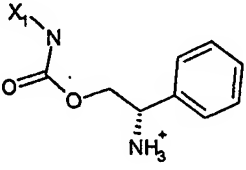
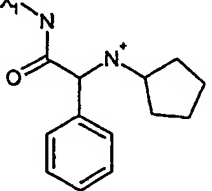
421	 <chem>CCN(Cc1ccccc1)C(=O)N*</chem>
422	 <chem>c1ccc(cc1)-c2ccc(cc2)C(=O)N*</chem>
423	 <chem>CS(=O)(=O)c1ccc(cc1)C(=O)N*</chem>
424	 <chem>Cc1ncsc1CCOC(=O)N*</chem>
425	 <chem>c1ccccc1[C@H](C)COC(=O)N*</chem>
426	 <chem>c1ccccc1C(N+2CCCC2)C(=O)N*</chem>

Table V

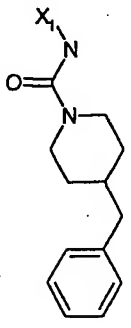
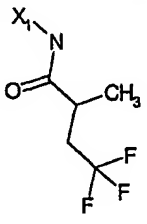
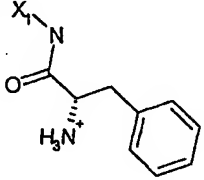
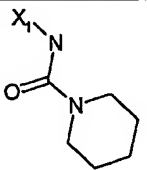
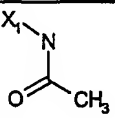
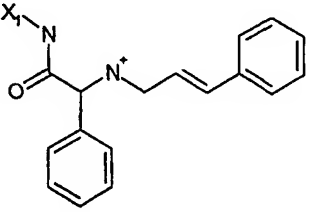
427	
428	
429	
430	
431	
432	

Table V

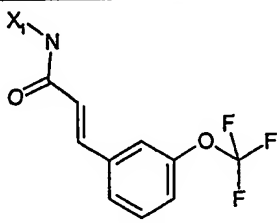
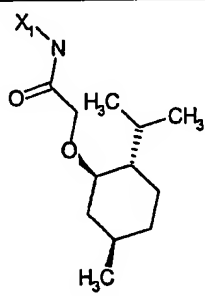
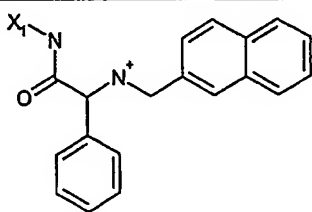
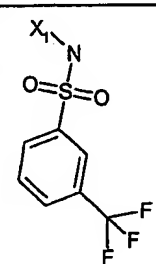
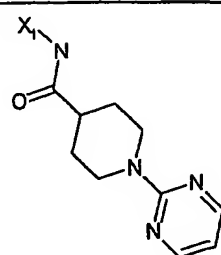

433	
434	
435	
436	
437	
438	



Table V

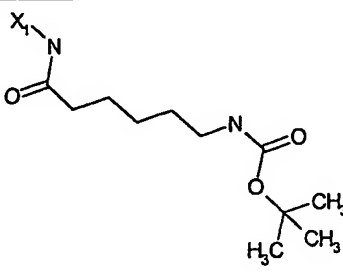
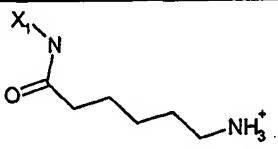
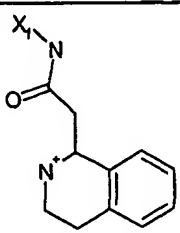
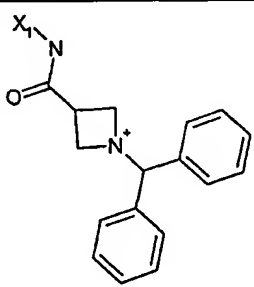
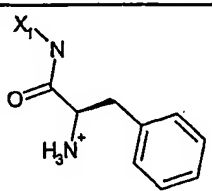
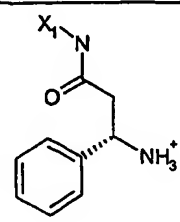
439	
440	
441	
442	
443	
444	

Table V

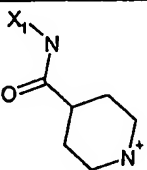
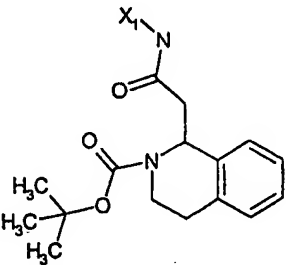
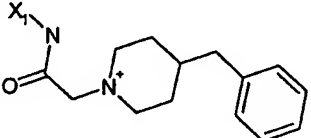
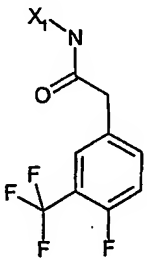
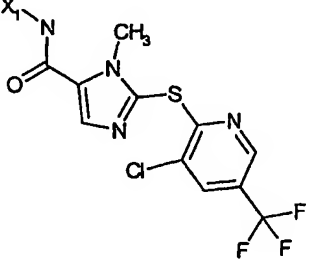
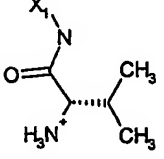
445	
446	
447	
448	
449	
450	

Table V

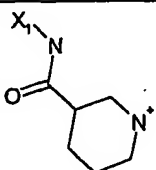
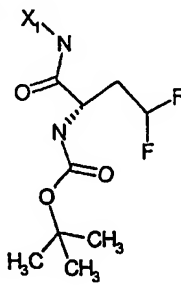
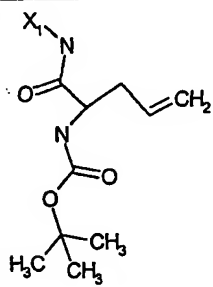
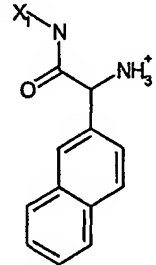
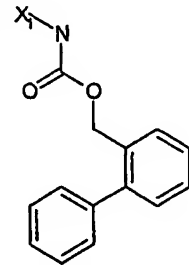
451	
452	
453	
598	
599	

Table V

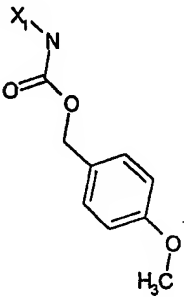
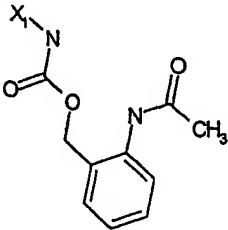
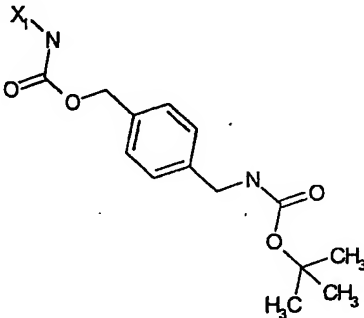
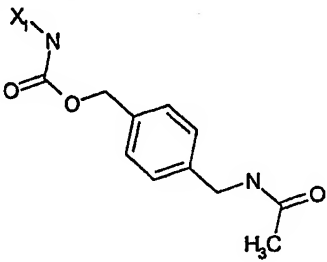
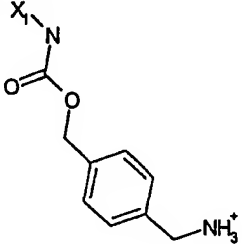
600	
601	
602	
603	
604	

Table V

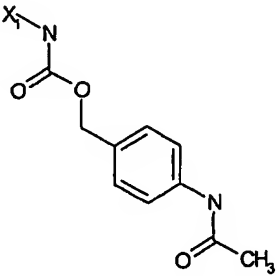
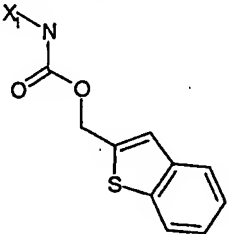
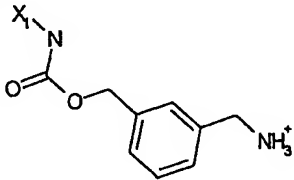
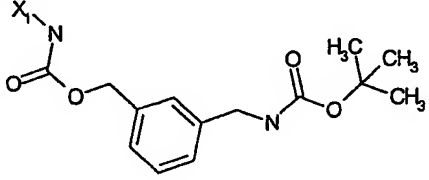
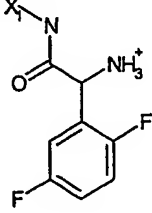
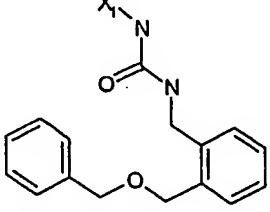
605	
606	
607	
608	
609	
610	

Table V

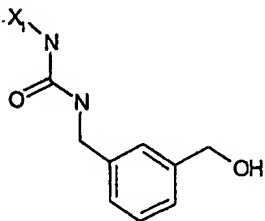
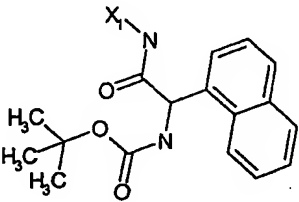
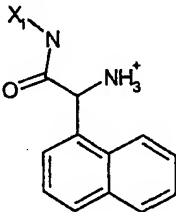
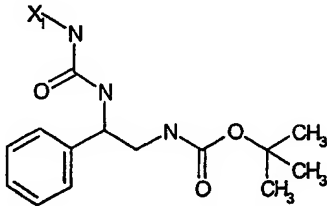
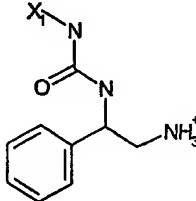
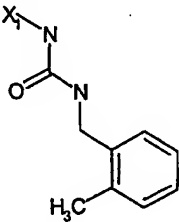
611	
612	
613	
614	
615	
616	

Table V

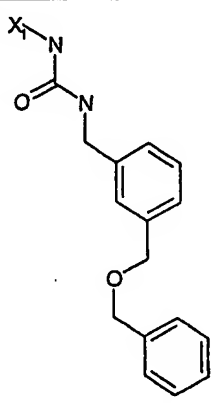
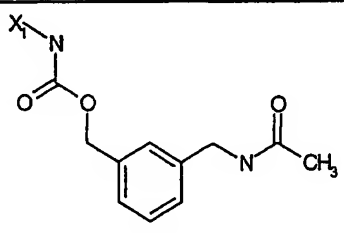
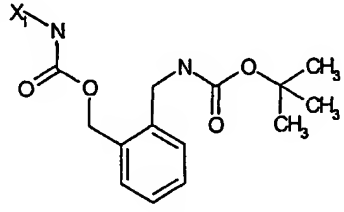
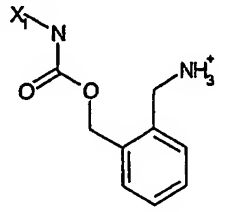
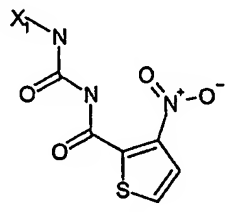
617	
618	
619	
620	
621	

Table V

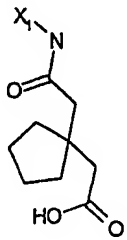
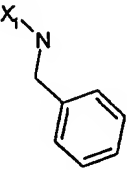
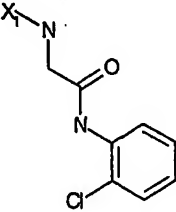
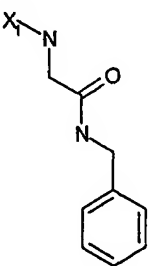
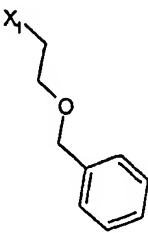
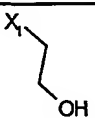
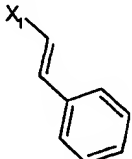
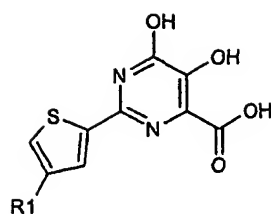
622	
623	
624	
625	
626	
627	
9 (Compound No. 628)	

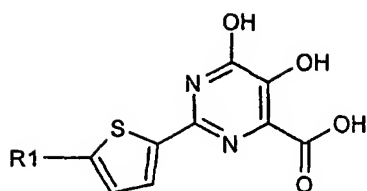


Table VI



Ex. No.	R1
454	
455	
456	
457	
458	

Table VIIa

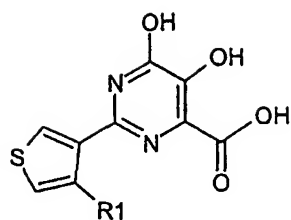


Ex. No.	R1
459	
460	
461	

Table VIIb

462	<p>Chemical structure of a pyrimidine derivative. The pyrimidine ring is substituted with a benzothienyl group at position 2 and a carboxylic acid group at position 4. The pyrimidine ring has hydroxyl groups at positions 6 and 7.</p>
-----	---

Table VIII



Ex. No.	R1
463	
464	
465	
466	
467	

Table VIII

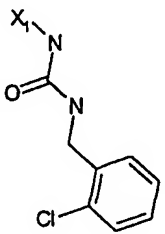
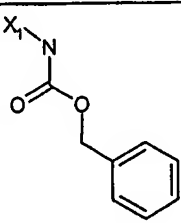

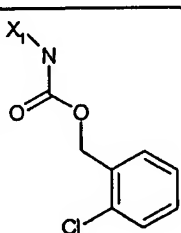
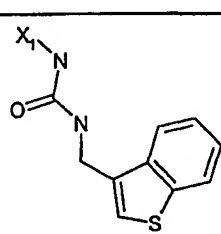
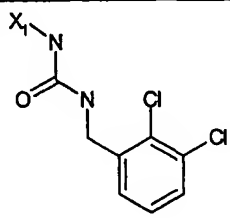
7 (Compound No. 36)	
469	
470	
471	
472	
473	

Table VIII

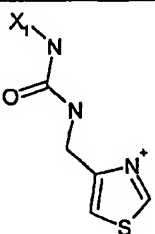
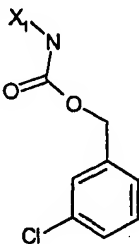
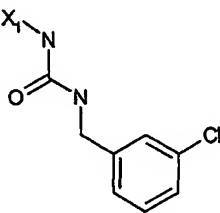
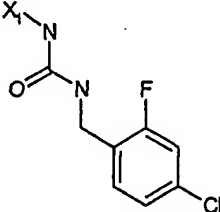
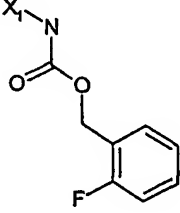
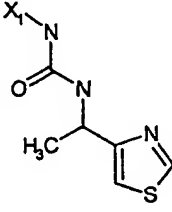
474	
475	
476	
477	
478	
479	

Table VIII

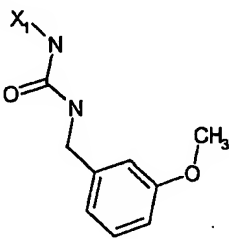
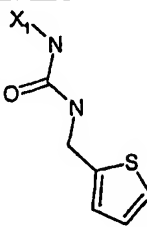
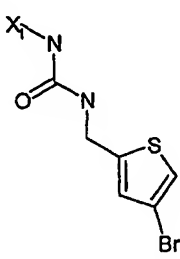
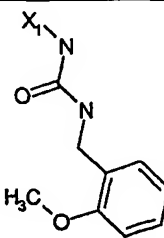
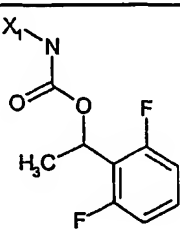
480	
481	
482	
483	
484	

Table VIII

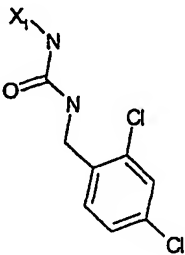
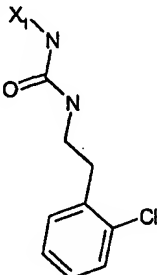
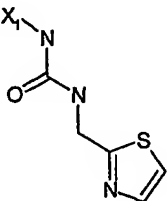
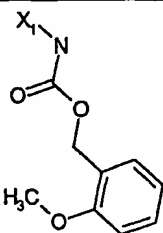
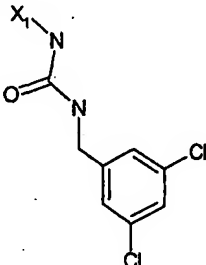
485	
486	
487	
488	
489	

Table VIII

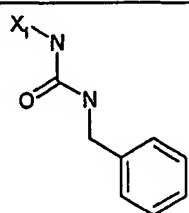
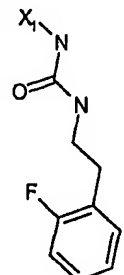
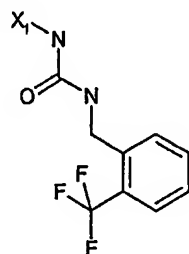
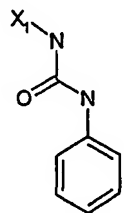
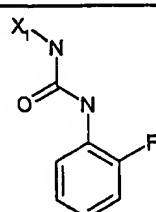
490	
491	
492	
493	
494	



Table VIII

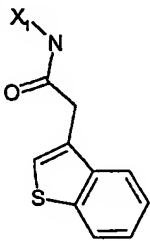
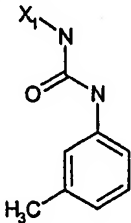
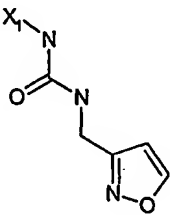
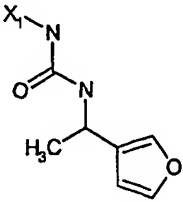
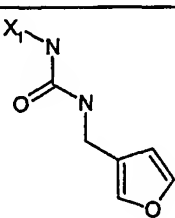
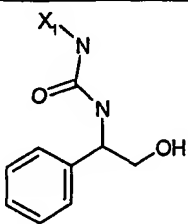
495	
496	
497	
498	
499	
500	

Table VIII

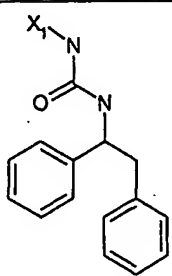
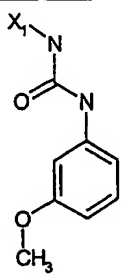
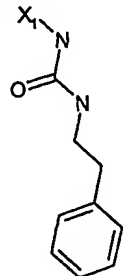
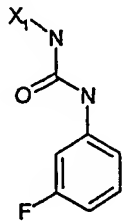
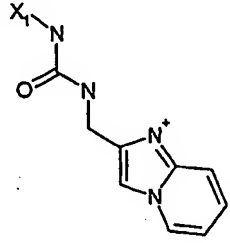
501	
502	
503	
504	
505	

Table VIII

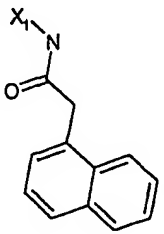
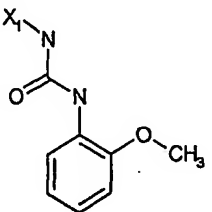
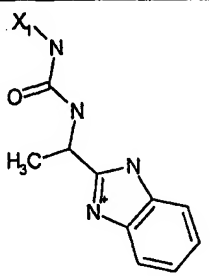
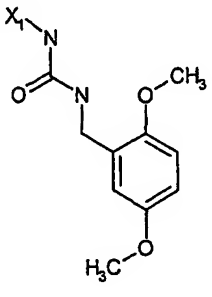
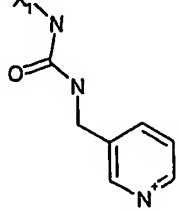
506	
507	
508	
509	
510	

Table VIII

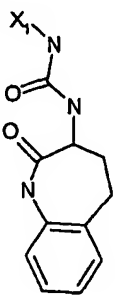
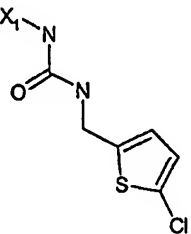
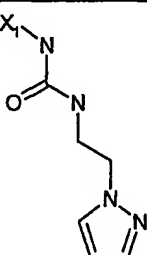
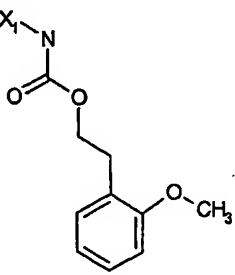
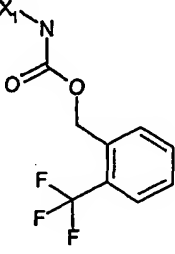
511	
512	
513	
514	
515	

Table VIII

516	
517	
518	
519	

Table VIII

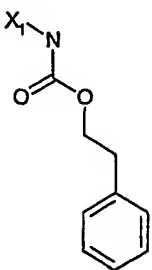
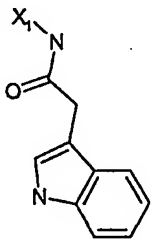
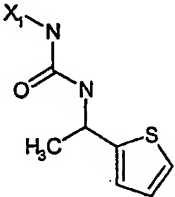
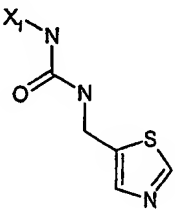
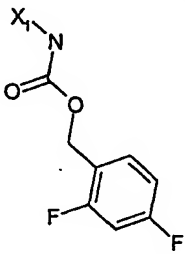
520	
521	
522	
523	
524	

Table VIII

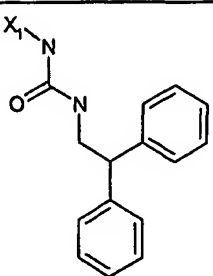
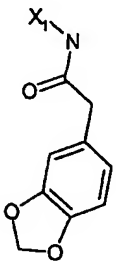
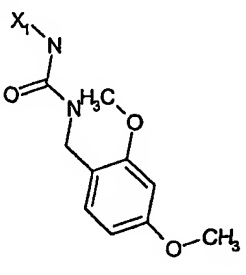
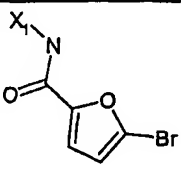
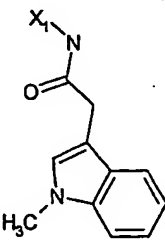
525	
526	
527	
528	
529	

Table VIII

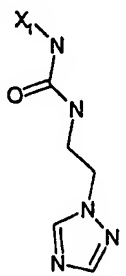
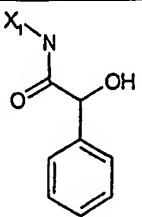
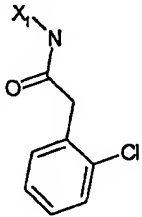
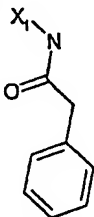
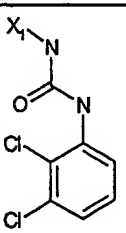
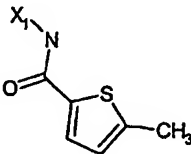
530	 <chem>X1N(C(=O)NCC1=NC=CN1)C(=O)N</chem>
531	 <chem>X1N(C(=O)C(O)c2ccccc2)C(=O)N</chem>
532	 <chem>X1N(C(=O)Cc2ccccc2Cl)C(=O)N</chem>
533	 <chem>X1N(C(=O)Cc2ccccc2)C(=O)N</chem>
534	 <chem>X1N(C(=O)Nc2cc(Cl)c(Cl)cc2)C(=O)N</chem>
535	 <chem>X1N(C(=O)c2cc(C)sc2)C(=O)N</chem>



Table VIII

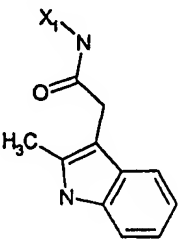
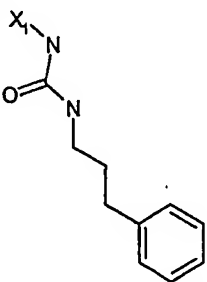
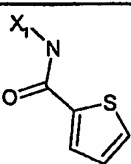
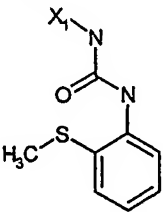
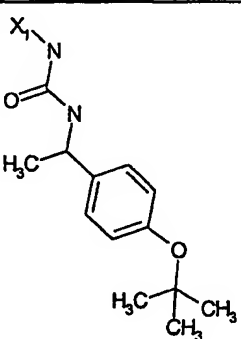
536	
537	
538	
539	
540	
541	$X_1-H$

Table VIII

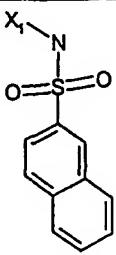
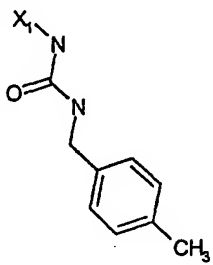
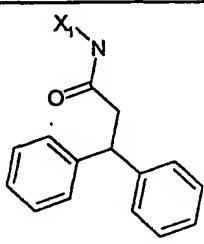
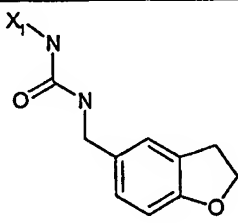
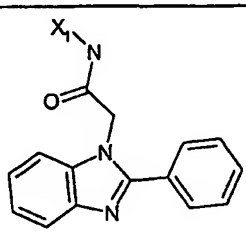
542	
543	
544	
545	
546	

Table VIII

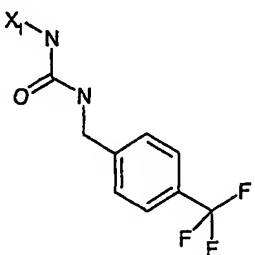
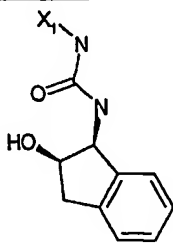
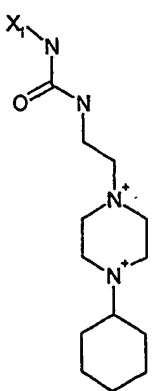
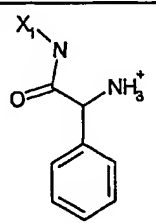
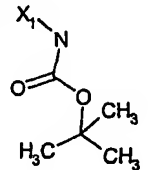
547	
548	
549	$X_1-NH_3^+$
550	
551	
552	

Table VIII

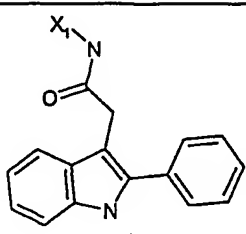
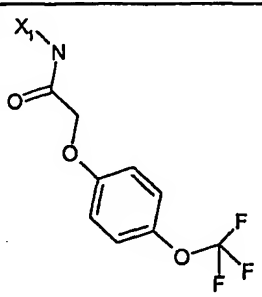
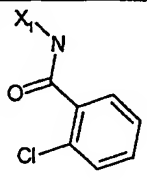
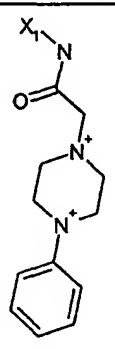
553	 <chem>X1NC(=O)Cc1c[nH]c2ccccc12-c3ccccc3</chem>
554	 <chem>X1NC(=O)COc1ccc(OC(F)(F)F)cc1</chem>
555	 <chem>X1NC(=O)Cc1c[nH]c2cc(Cl)ccc12</chem>
556	 <chem>X1NC(=O)CN1CCN(C1)c2ccccc2</chem>

Table VIII

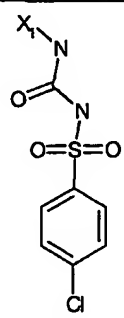
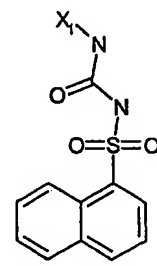
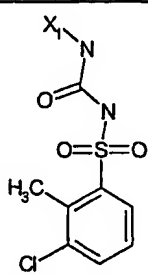
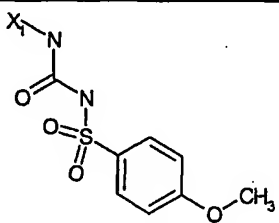
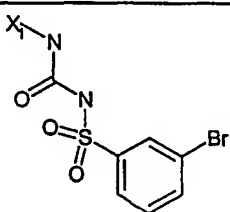
629	
8 (Compound No. 630)	
631	
632	
633	

Table VIII

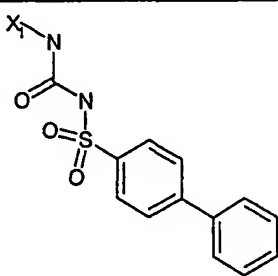
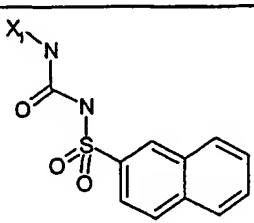
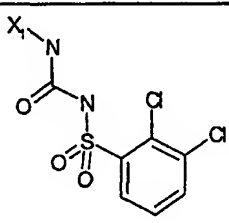
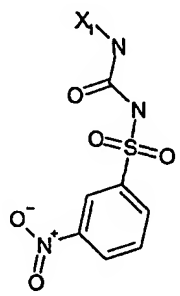
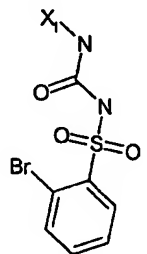
634	
635	
636	
637	
638	

Table VIII

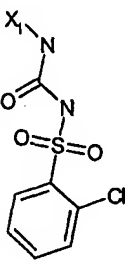
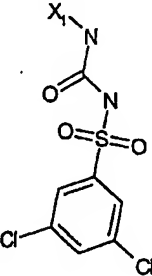
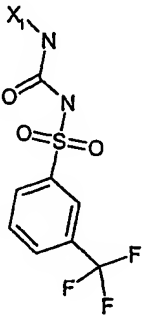
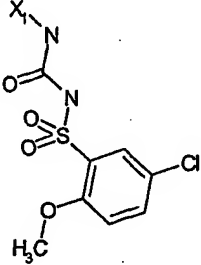
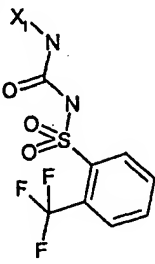
639	
640	
641	
642	
643	

Table VIII

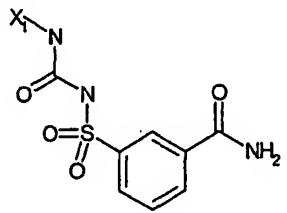
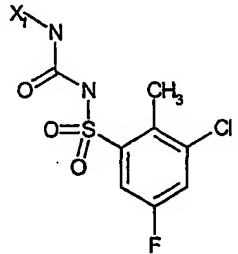
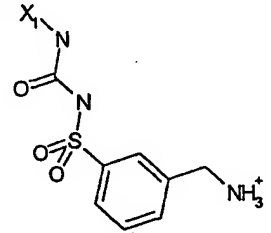
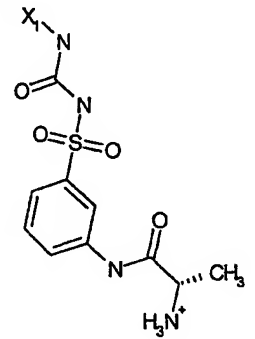
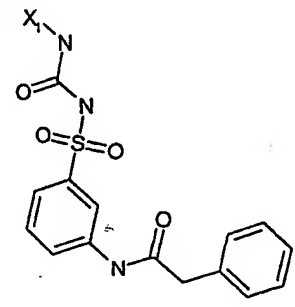
644	
645	
646	
647	
648	



Table VIII

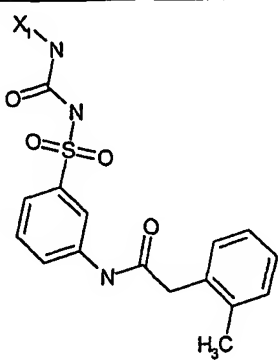
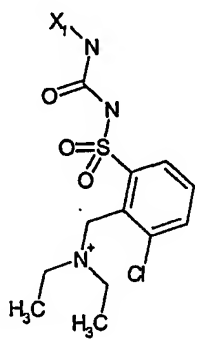
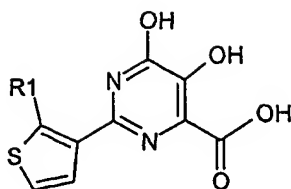
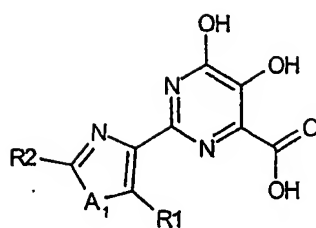
649	
650	

Table IX



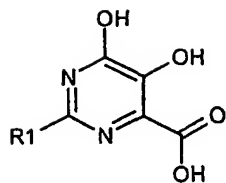
Ex. No.	R1
557	
558	
651	
652	

Table X



Ex. No.	A1	R1	R2
559	S		$X_2-H$
560	O		$X_2-H$
561	O		$X_2-H$
562	S	$X_1-H$	$H_3C-X_2$

Table XI



Ex. No.	R1
563	<p>Chemical structure of a thiazole ring with substituent X1 at position 2.</p>
564	<p>Chemical structure of a furan ring with substituent X1 at position 2.</p>
565	<p>Chemical structure of a pyrimidine ring with substituent X1 at position 2.</p>
566	<p>Chemical structure of a quinoline ring with substituent X1 at position 2.</p>
567	<p>Chemical structure of an indole ring with substituent X1 at position 2.</p>
568	<p>Chemical structure of an isoxazole ring with substituents H<sub>3</sub>C and X1.</p>
569	<p>Chemical structure of a 1,3-bis(hydroxymethyl)propane derivative with substituent X1.</p>
570	<p>Chemical structure of a purine ring with substituents H<sub>3</sub>C and X1.</p>
571	<p>Chemical structure of a pyrimidine ring with substituents X1 and NH<sub>3</sub><sup>+</sup>.</p>

Table XI

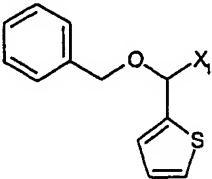
572	
-----	---

Table XIIa

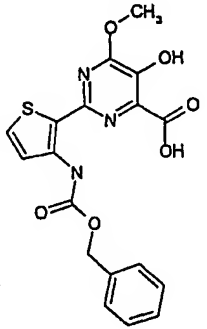
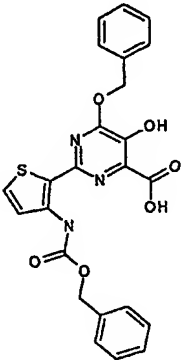
Ex. No.	
573	
574	

Table XIIb

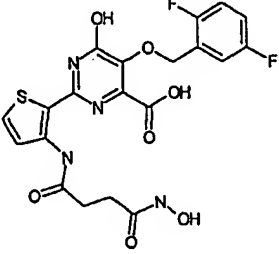
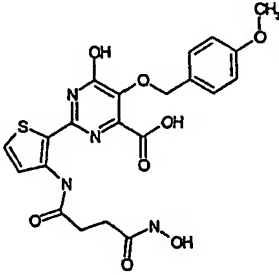
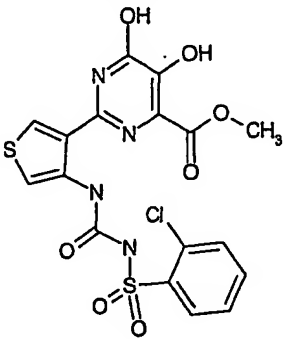
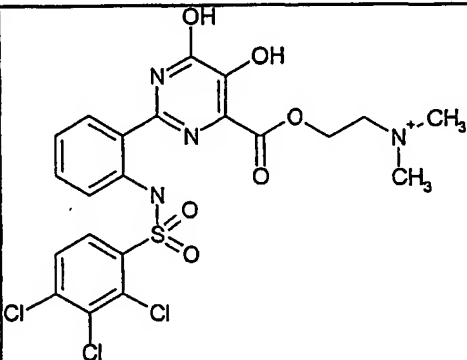
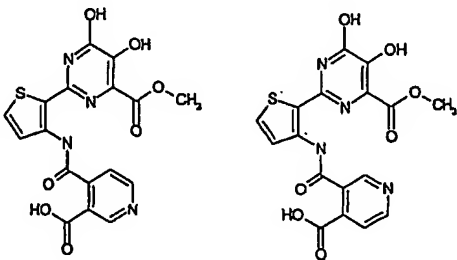
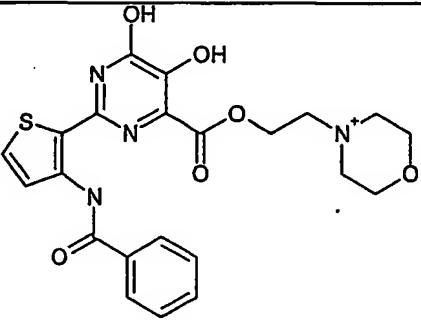
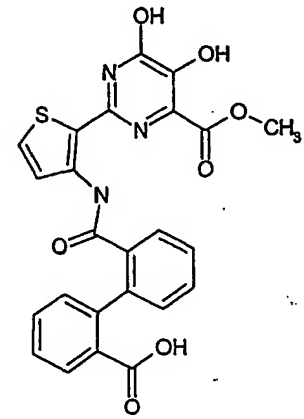
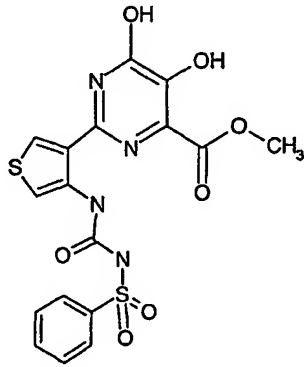
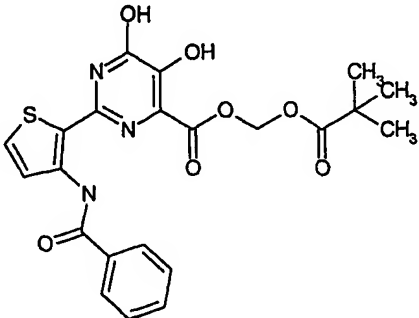
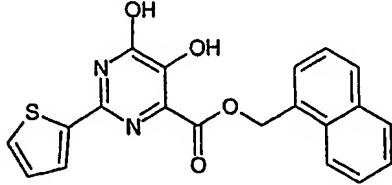
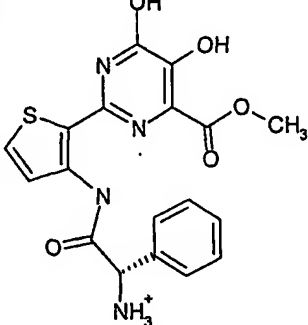
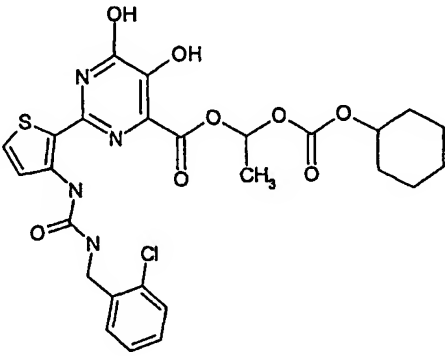
575	
576	

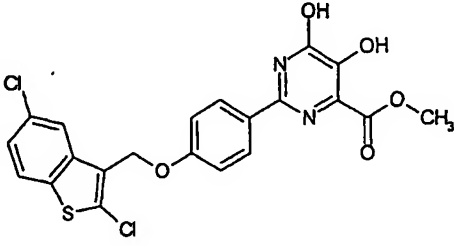
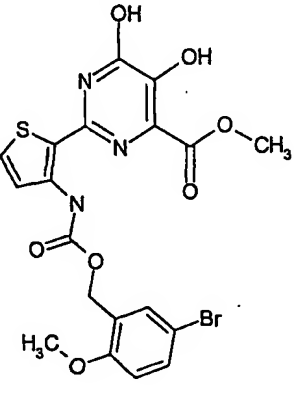
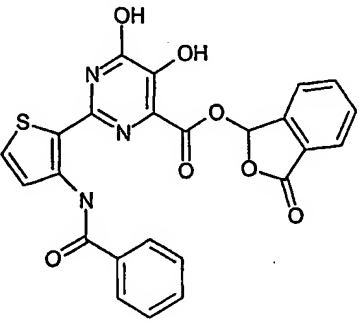
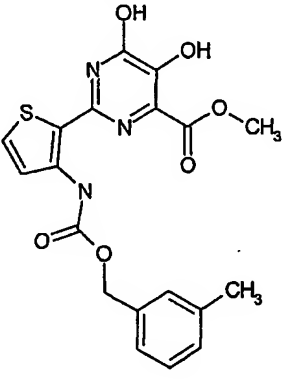
Table XIc

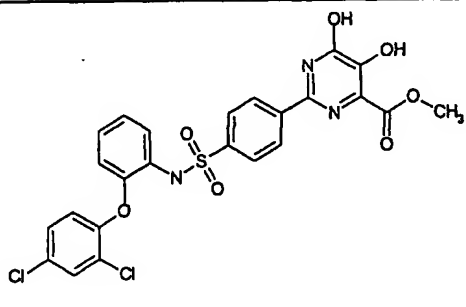
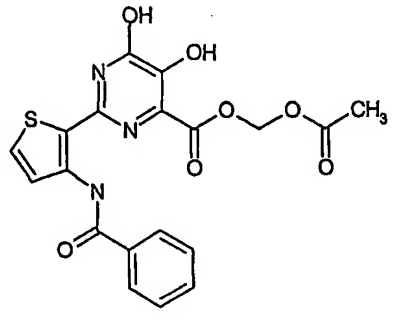
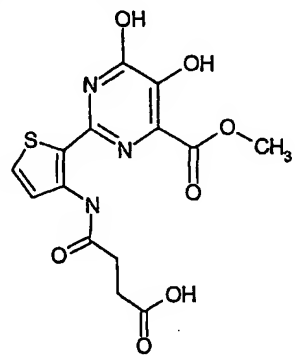
Ex. No.	
577	
578	
579	

580	
581	
582	



583	 <chem>CC(C)(C)C(=O)OCCOC(=O)c1nc(O)c(O)n(c1-c1ccsc1)N(C(=O)c2ccccc2)c3ccccc3</chem>
584	 <chem>Oc1nc(O)c(O)n(c1-c1ccsc1)C(=O)OCCc2cc3ccccc3cc2</chem>
585	 <chem>COC(=O)c1nc(O)c(O)n(c1-c1ccsc1)N(C(=O)C(N)Cc2ccccc2)c3ccccc3</chem>
586	 <chem>CCOC(=O)OC(=O)OC(=O)c1nc(O)c(O)n(c1-c1ccsc1)N(C(=O)NCCc2ccccc2Cl)c3ccccc3</chem>

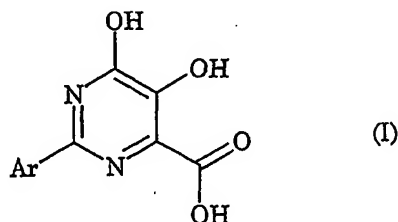
587	 <chem>COC(=O)c1c(O)c(O)nnc1C2=CC=C(OC2Cc3cc(Cl)cc(Cl)s3)O</chem>
588	 <chem>COC(=O)c1c(O)c(O)nnc1C2=CC=C(S2)C(=O)OC3=CC=C(Br)C(OC)=C3</chem>
589	 <chem>O=C1C(=O)OC2=CC=CC=C2C1OC(=O)c1c(O)c(O)nnc1C2=CC=C(S2)C(=O)OC3=CC=CC=C3</chem>
590	 <chem>COC(=O)c1c(O)c(O)nnc1C2=CC=C(S2)C(=O)OC3=CC=C(C)C=C3</chem>

591	 <chem>COC(=O)c1nc(C2=CC=CC=C2S(=O)(=O)N2C(=C(Cl)C(Cl)=C2)C3=CC=CC=C3)c(O)c(O)n1</chem>
592	 <chem>CC(=O)OCCOC(=O)c1nc(C2=CC=CSC2C(=O)N2C(=O)C3=CC=CC=C3)c(O)c(O)n1</chem>
593	 <chem>COC(=O)c1nc(C2=CC=CSC2C(=O)N2C(=O)CC(=O)O)c(O)c(O)n1</chem>

**CLAIMS:**

1. A compound of formula (I), or a tautomer thereof, as well as pharmaceutically acceptable salts and esters thereof:

5



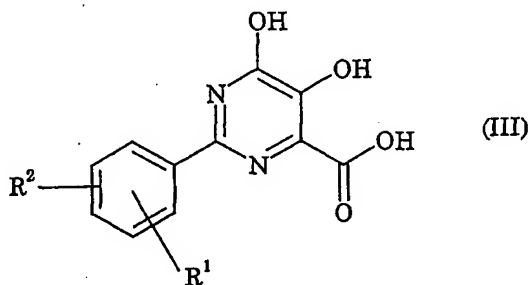
in which Ar is an optionally substituted aryl group.

2. A compound as claimed in claim 1 wherein Ar represents phenyl, thienyl, oxazolyl, thiazolyl, furyl, isoquinolinyl, indolyl, isoxazolyl, pyrazolopyrimidinyl or pyrazinyl, any of which groups may be optionally substituted.

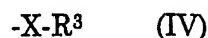
3. A compound as claimed in claim 2 wherein Ar represents optionally substituted phenyl.

4. A compound as claimed in claim 3 represented by formula (III), or a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof:

20



wherein  $R^1$  and  $R^2$  are each independently selected from hydrogen and a substituent group of formula (IV):



5

in which

X is selected from  $-NH-SO_2-$ ,  $-NH-SO_2-NH-$ ,  $-CH_2-SO_2-$ ,  $-SO_2-NH-$ ,  $-NH-CO-NH-$ ,  $-NH-CS-NH-$ ,  $-NH-CO-O-$ ,  $-NH-CO-$ ,  $-CO-NH-$ ,  $-NH-CO-NH-SO_2-$ ,  $-NH-CO-NH-CO-$ ,  $-O-$ ,  $-S-$ ,  $-NH-$ ,  $-CH_2-$ ,  $-CH_2O-$  and  $-CH_2S-$ ; and

10

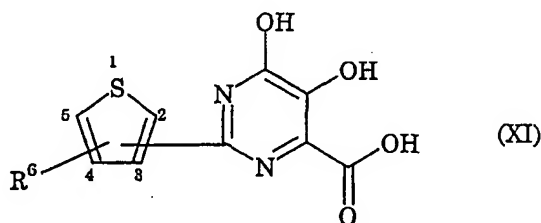
$R^3$  represents aryl, aralkyl, cycloalkyl, lower alkyl, heterocycloalkyl, lower alkenyl, cycloalkenyl or heterocycloalkenyl, any of which groups may be optionally substituted.

15

5. A compound as claimed in claim 2 wherein Ar represents optionally substituted thienyl.

20

6. A compound as claimed in claim 5 represented by formula (XI), or a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof:



25

wherein  $R^6$  represents hydrogen or a group of formula (IV) as defined in claim 4.

7. A compound of formula (I) as defined in claim 1 which is derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy

groups, or a tautomer thereof, as well as pharmaceutically acceptable salts and esters thereof.

8. A compound selected from Example Nos. 1-7, 42-467, 469-568  
5 and 570-593, or a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof.

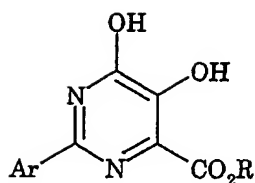
9. A compound selected from Example Nos. 8, 9, 594-627, 629  
10 and 631-652, or a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof.

10. A compound of formula (I) as defined in claim 1, or a  
compound of formula (I) which is derivatised at one or more of the  
4-hydroxy, 5-hydroxy or 6-carboxy groups, or a tautomer thereof, or a  
15 pharmaceutically acceptable salt or ester thereof, for use in therapy.

11. A pharmaceutical composition comprising a compound of  
formula (I) as defined in claim 1, a compound of formula (I) which is  
derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy  
20 groups, or a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof, in association with a pharmaceutically acceptable carrier.

12. The use of a compound of formula (I) as defined in claim 1, of  
a compound of formula (I) which is derivatised at one or more of the 4-  
25 hydroxy, 5-hydroxy or 6-carboxy groups, of a tautomer thereof, or of a pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament for treatment or prevention of infection by hepatitis C virus.

13. A process for the preparation of a compound of formula (I) as  
30 defined in claim 1, which comprises hydrolysis of the corresponding methyl or other ester of formula 2:



2

where R is a methyl or other lower alkyl group.

5

14. A method of inhibiting hepatitis C virus polymerase and/or of treating or preventing an illness due to hepatitis C virus, the method involving administering to a subject suffering from the condition a therapeutically or prophylactically effective amount of a compound of formula (I) as defined in claim 1, a compound of formula (I) which is derivatised at one or more of the 4-hydroxy, 5-hydroxy or 6-carboxy groups, a tautomer thereof, or a pharmaceutically acceptable salt or ester thereof.

10

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 01/07955

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/557 A61K31/505 C07D409/04 C07D417/04 C07D409/14  
A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 05159 A (HOECHST AG) 2 April 1992 (1992-04-02) Compound 1.154, page 58 claim 1	7
X	CULBERTSON, TOWNLEY P.: "Synthesis of 5,6-Dihydroxy-2-phenyl-4-pyrimidinecarboxy- lic Acid. Methyl Ester, a Corrected Structure" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 16, no. 7, 1979, pages 1423-1424, XP001029094 Compounds 4a-c and 6.	1-4,7,8, 11,13
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

19 October 2001

Date of mailing of the international search report

02/11/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Uselli, A



## INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/EP 01/07955

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SANTILLI, ARTHUR A.; SCOTese, ANTHONY C.: "Synthesis of 1,2,4-Oxadiazines and Their Rearrangement to Pyrimidines" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 16, no. 2, 1979, pages 213-216, XP001029092 Scheme I -----	7
A	DE 198 17 265 A (BAYER AG) 21 October 1999 (1999-10-21) page 1, line 1 -page 3, line 47; claim 1 -----	1-14
A	WO 00 13708 A (BAILEY THOMAS R ;VIROPHARMA INC (US); YOUNG DOROTHY C (US)) 16 March 2000 (2000-03-16) page 3, line 30 -page 6, line 12; claim 1 -----	1-14

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/07955

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9205159	A	02-04-1992	DE 4029654 A1	02-04-1992
			WO 9205159 A1	02-04-1992
			ZA 9107429 A	27-05-1992
DE 19817265	A	21-10-1999	DE 19817265 A1	21-10-1999
			AU 3813499 A	08-11-1999
			WO 9954312 A1	28-10-1999
			EP 1073642 A1	07-02-2001
WO 0013708	A	16-03-2000	AU 6137099 A	27-03-2000
			EP 1109580 A1	27-06-2001
			WO 0013708 A1	16-03-2000